

Short communication

Circulating levels of brain-derived neurotrophic factor correlate with disease severity in the intrinsic type of atopic dermatitis

Background: Recent studies have shed light on the complex regulation of genetic, environmental, immunologic and pharmacologic factors, which contribute to the development of atopic dermatitis (AD). However, it is still unclear to which extent neuroimmune mediators have a role in AD.

Aims of the study: To assess peripheral neurotrophin levels and their correlation with scoring atopic dermatitis (SCORAD) scores in both the intrinsic and extrinsic types of AD compared with patients with psoriasis and nonatopic healthy subjects.

Methods: Levels of brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) were assessed in peripheral blood with enzyme-linked immunosorbent assay. Based on IgE-mediated sensitization, AD was divided into the extrinsic and intrinsic type. Severity of AD was assessed with SCORAD score and with psoriasis area and severity index (PASI) in patients with psoriasis.

Results: Brain-derived neurotrophic factor and NGF were detectable in all the subjects studied. However, the levels of both neurotrophins were significantly higher in patients with extrinsic and intrinsic types of AD compared with patients with psoriasis and nonatopic healthy subjects (NGF: $P < 0.001$, BDNF: $P < 0.001$). NGF and BDNF levels were similar in the intrinsic and extrinsic type of AD. There was a significant correlation between BDNF and SCORAD score only in patients with the intrinsic type of AD ($r = 0.57$, $P < 0.05$).

Conclusions: This study shows for the first time that NGF and BDNF are increased in both, the extrinsic type and the intrinsic type of AD. This finding points to a similar pathophysiologic background implicating a neuroimmune network in both variants of this chronic inflammatory skin disease. Future studies are needed to show the direct mechanisms of neurotrophin action in chronic inflammatory skin.

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Atopic dermatitis (AD) is a chronically relapsing inflammatory skin disease characterized by eczematous skin lesions and intense pruritus that often occur in early childhood but can also start or persist in adulthood. Recent studies have shed light on the complex regulation of genetic, environmental, immunologic and pharmacologic factors, which contribute to the development of AD (1). Based on IgE-mediated sensitization, AD is subdivided into two subtypes, the extrinsic type and the intrinsic type (2). In contrast to the intrinsic type, the extrinsic type of AD is characterized by increased levels of total IgE, allergen-specific IgE antibodies, positive history for allergic rhinitis and asthma. Interestingly, both types display the same clinical features such as, typical morphology, nonspecific cutaneous hyperreactivity, pruritus and are distinguished only by immunological parameters. The contribution of T cells, antigen-present-

ing cells, eosinophils and microbial superantigens to the pathophysiology of AD is well established. In contrast, neuroimmune interactions in this chronic inflammatory skin disease still remain to be elucidated. Therefore, the aim of this study was to compare the nerve growth factor (NGF) and the brain-derived neurotrophic factor (BDNF) levels as possible mediators for neuroimmune interactions, in both the intrinsic type and the extrinsic type of AD, patients with psoriasis and nonatopic healthy subjects.

Methods

Patients

After obtaining informed consent (approved by the local ethics committee), peripheral venous blood was obtained at 9 am to prevent daily variations. Patients with the extrinsic type of AD ($n = 22$; mean age 31 ± 10 years, mean SCORAD score 22.0 ± 11.2 , positive history of intermittent allergic rhinitis, IgE-mediated sensitization to at least three out of 10 common aeroallergens) and

Abbreviations: AD, atopic dermatitis; BDNF, Brain-derived neurotrophic factor; NGF, nerve growth factor.

intrinsic type of AD ($n = 18$, mean age 30 ± 15 years, mean SCORAD score 18.8 ± 7.5 , no history of allergic rhinitis or allergic asthma; no IgE-mediated sensitization to aeroallergens), defined according to the criteria of Hanifin and Rajka were included in the study. In addition, we included 23 patients with psoriasis (mean age 29 ± 7 years, mean PASI 5.0 ± 8.2) and 33 nonatopic healthy subjects (mean age 36 ± 13 years). Subjects did not receive systemic or local immunosuppressive treatment.

Analysis of BDNF and NGF levels

Commercial enzyme-linked immunosorbent assays (NGF and BDNF; R&D Systems, Wiesbaden, Germany) were used to assess the BDNF and NGF serum levels, according to the manufacturer's recommendations. The specificity of the assays was confirmed by the manufacturers, the detection limit was 39 pg/ml for BDNF, and 23.4 pg/ml for NGF.

Statistical analysis

Statistical analysis was performed with the statistical software package SigmaStat (SigmaStat for Windows; Jandel Scientific Erkrath, Wiesbaden, Germany). Data were analyzed with either Student's *t*-test (normality test passed) or Mann-Whitney Rank Sum test (normality test failed). To assess the correlation between NGF, BDNF and SCORAD score or PASI a Pearson Product Moment Correlation (*r*; normality test passed) or a Spearman Rank Order Correlation (*r*_s; normality test failed) was performed. A *P*-value of <0.05 was considered to be statistically significant.

Results

High levels of NGF and BDNF in extrinsic and intrinsic AD

Brain-derived neurotrophic factor and NGF levels were detectable in all sera (Fig. 1). However, NGF serum levels were significantly higher in patients with extrinsic or intrinsic types of AD compared with nonatopic healthy subjects ($P < 0.001$) (Fig. 1A). In addition, NGF levels were higher in both phenotypes of AD compared with the patients with psoriasis ($P < 0.001$), whereas there was no difference in NGF levels between

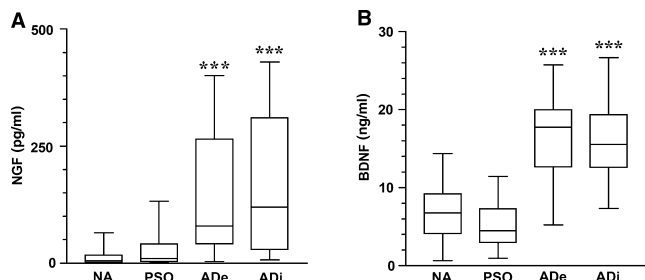


Figure 1. Significantly increased levels of nerve growth factor (A) and brain-derived neurotrophic factor (B) in patients with extrinsic (ADe, $n = 22$) and intrinsic (ADi, $n = 18$) type of AD compared with nonatopic healthy subjects (NA, $n = 33$) and patients with psoriasis (PSO, $n = 23$). Box plot graphs display the median (line within the box) interquartile range (edge of box), *** $P < 0.001$.

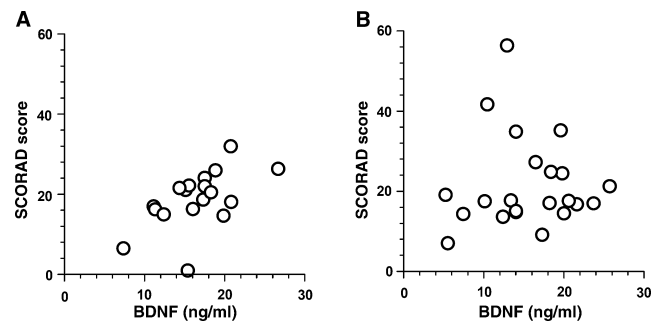


Figure 2. Significant correlation of BDNF levels (*x*-axis) with SCORAD score (*y*-axis) in patients with the intrinsic type of atopic dermatitis (A, $r = 0.57$, $P < 0.05$). No correlation of SCORAD score and BDNF levels in patients with atopic dermatitis of the extrinsic type (B, $r = 0.11$, $P = 0.69$).

the two subtypes of AD. The BDNF levels were higher in patients with the extrinsic or the intrinsic type of AD compared with nonatopic healthy subjects ($P < 0.001$) (Fig. 1B). Moreover, BDNF levels of AD patients were also higher in comparison with patients with psoriasis ($P < 0.001$). There was no statistically significant difference in BDNF levels between the intrinsic and extrinsic type of AD (Fig. 1B). In addition, we did not find a correlation between the BDNF/NGF levels in intrinsic and extrinsic AD and psoriasis (data not shown).

BDNF levels correlate with disease severity in intrinsic AD

We assessed a significant correlation of BDNF levels and SCORAD score in the intrinsic type of AD ($r = 0.57$, $P < 0.05$, Fig. 2A), whereas there was no correlation of BDNF levels and SCORAD score in the extrinsic type of AD ($r = 0.11$, $P = 0.69$, Fig. 2B). There was no significant correlation between the SCORAD score and the NGF levels in both phenotypes of AD (data not shown). In patients with psoriasis, PASI did not correlate with NGF or BDNF levels (data not shown).

Discussion

Neurotrophins have been assessed in allergic diseases such as allergic airway inflammation and their pivotal role has been described in several inflammatory and allergic conditions (3–5). It is well known that neurotrophins exert immunomodulatory functions not only on nerves but also on immune cells which are characterized best for the prototype of the neurotrophins NGF (6). Recently, it was shown by us that BDNF has a functional role on eosinophil granulocytes (7). Brain-derived neurotrophic factor induced chemotaxis and inhibited apoptosis of peripheral blood eosinophils of patients with the extrinsic type of AD, whereas BDNF had no functional effect on eosinophils derived from nonatopic healthy subjects. The possible mechanism of BDNF action is

likely to be explained by an increased neurotrophin receptor upregulation such as tyrosine kinase (trk)B and pan-neurotrophin receptor p75^{NTR} in peripheral blood eosinophils of AD. In the latter study, we also found increased levels of BDNF in patients with the extrinsic type of AD compared with nonatopic subjects. Brain-derived neurotrophic factor is released by platelets, therefore, a release in serum could be likely explained by platelet activation (8). However, BDNF levels were significantly increased in both serum and plasma in the extrinsic AD compared with the healthy subjects in our recent study (7). Therefore, we assessed the NGF and the BDNF levels in serum in this study. Toyoda et al. (9), described increased levels of NGF and substance P (SP) in AD (not differentiated into intrinsic or extrinsic type) correlating with disease activity. In the present study, however, we found no correlation of NGF and BDNF levels with disease activity in the extrinsic type of AD. On the other hand, there was a significant correlation between the BDNF levels and the SCORAD score in the intrinsic type of AD. So far, we have no explanation why BDNF levels correlate with disease severity only in the intrinsic type of AD. It is likely that in addition to immunological differences, neurotrophic mediators play a more prominent role in the intrinsic phenotype of AD. Interestingly, neurotrophin levels were increased in AD

irrespective of the presence of specific sensitization. These data add some new evidence for a similar pathophysiological background in intrinsic and extrinsic AD, pointing to possible neuroimmune interactions (10). In this regard, it is interesting to note that we did not find increased levels of NGF or BDNF in patients with psoriasis. This underlines, that not inflammation *per se*, but especially atopic inflammatory reactions are associated with increased peripheral neurotrophin levels. Still, the cellular source responsible for increased BDNF and NGF levels has to be assessed. In this regard, eosinophil granulocytes, macrophages but also endothelial cells represent the possible sources of neurotrophin (11–14).

Nerve growth factor and BDNF promote hematopoietic colony growth and participate in wound healing and tissue repair, contributing to skin or airway remodeling in inflammatory conditions (15). In this regard, our observations may have important implications for the role of neurotrophins in skin remodeling, mucosal immunity and inflammation, especially in AD.

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