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ORIGINAL PAPER

Avenanthramides, polyphenols from oats, exhibit anti-inflammatory and anti-itch activity

Runa Sur · Anu Nigam · Devon Grote · Frank Liebel · Michael D. Southall

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Abstract Oatmeal has been used for centuries as a soothing agent to relieve itch and irritation associated with various xerotic dermatoses; however few studies have sought to identify the active phytochemical(s) in oat that mediate this anti-inflammatory activity. Avenanthramides are phenolic compounds present in oats at approximately 300 parts per million (ppm) and have been reported to exhibit anti-oxidant activity in various cell-types. In the current study we investigated whether these compounds exert anti-inflammatory activity in the skin. We found that avenanthramides at concentrations as low as 1 parts per billion inhibited the degradation of inhibitor of nuclear factor kappa B-α (IκB-α) in keratinocytes which correlated with decreased phosphorylation of p65 subunit of nuclear factor kappa B (NF-κB). Furthermore, cells treated with avenanthramides showed a significant inhibition of tumor necrosis factor-α (TNF-α) induced NF-κB luciferase activity and subsequent reduction of interleukin-8 (IL-8) release. Additionally, topical application of 1–3 ppm avenanthramides mitigated inflammation in murine models of contact hypersensitivity and neurogenic inflammation and reduced pruritogen-induced scratching in a murine itch model. Taken together these results demonstrate that avenanthramides are potent anti-inflammatory agents that appear to mediate the anti-irritant effects of oats.

Keywords Inflammation · Itch · Avenanthramide · Cytokine · NF-κB · Keratinocyte

R. Sur · A. Nigam · D. Grote · F. Liebel · M. D. Southall (✉)
Preclinical Pharmacology, Skin Research Center,
Johnson & Johnson Consumer Products,
199 Grandview Road, Skillman, NJ 08558, USA
e-mail: msoutha@cpcus.jnj.com

Abbreviations

RTX	Resiniferatoxin
TNFα	Tumor necrosis factor-α
IL-8	Interleukin-8
NF-κB	Nuclear factor kappa beta

Introduction

Ancient literature describes the anti-inflammatory and anti-itch properties of oat extracts. Medical texts by Pliny and other notables promoted the topical application of oatmeal flour for a variety of dermatologic conditions [17]. The range of clinical applications for colloidal oatmeal in dermatologic practice is most often as adjunctive therapy in pruritic skin conditions such as atopic dermatitis [9, 12, 25, 30] and allergic or irritant contact dermatitis [9, 10, 25, 30]. The direct anti-irritant activity of oats has been well established both in vitro and in clinical studies. Extracts of oats have been shown to decrease the ionophore stimulated liberation of arachidonic acid from phospholipids in keratinocytes [2] and inhibit prostaglandin biosynthesis [28]. In addition, Vie and co-workers [32] demonstrated that topical application of oat extracts (*Avena sativa*) significantly decreased inflammation on the volar forearm of human subjects induced by sodium lauryl sulfate. Despite the widespread use for skin irritation, few studies have examined the phytochemicals present in oat that mediate the anti-inflammatory activity.

The composition of oats is predominantly starch (65–85%), proteins (15–20%, including enzymes), lipids (3–11%), and about 5% each of fiber and beta glucans. Avenanthramides are a family of 20 structurally related low molecular weight soluble phenolic compounds that are found in oats [8] at up to 300 parts per million (ppm), or

0.03%. Thus, based on compositions, avenanthramides are a minor constituent of oats. Oats have been shown to de novo produce avenanthramides. Hydroxycinnamoyl-CoA:hydroxyanthranilate *N*-hydroxycinnamoyltransferase (HHT), which catalyzes the final condensation reaction to produce avenanthramides, has been localized in oat leaves [14] and oat seeds [22] and feeding of oat leaves with labeled L-phenylalanine and anthranilic acid revealed that avenanthramides are produced from these precursors [15]. The primary role for avenanthramides may relate to host protection since these compounds appear to exert antimicrobial activity. Indeed infection of oats with the crown rust fungus (*Puccinia coronata*) has been shown to induce production of avenanthramides and this increase in avenanthramides results in an inhibition of fungal growth [23, 24]. Avenanthramides have been reported to exhibit antioxidant activity in vitro [6] and among all oat phenolic antioxidant compounds, avenanthramides are being studied intensely because they have 10–30 times the antioxidant activity of other phenolics such as vanillin and caffeic acid [11]. Finally, avenanthramides are orally bioavailable in humans [7] and the antioxidant activity from ingestion of avenanthramides is believed to mediate the cardioprotective effects of oats [20]. In this study we sought to determine whether avenanthramides exert anti-inflammatory activity and examine the mechanism of the anti-inflammatory activity in human keratinocytes.

Materials and methods

Materials

Avenanthramides isolated from *Avena sativa* (oats) and enriched to a concentration of 100 ppm were obtained from Symrise Chemical (Holzminden, Germany). Oxazolone, Resiniferatoxin, Compound 48/80 and all routine reagents were obtained from Sigma (Sigma Aldrich, St Louis, MO, USA). TNF-α was purchased from Preprotech (Rocky Hill, NJ, USA). Female ICR mice approximately 8–10 weeks old (Taconic, Germantown, NY, USA) were housed five per cage and maintained on a 12-h dark/light cycle with food and water ad libitum. The Institutional Animal Care and Use Committee at Johnson & Johnson approved all procedures used in these experiments.

Cells and cell culture

Normal human epidermal neonatal keratinocytes were obtained from Cascade Biologics (Portland, OR, USA) and maintained in serum-free Epilife medium (Cascade Biologics; Portland, OR, USA) supplemented with human keratinocyte growth supplement containing 0.2% (v/v) bovine pituitary extract (BPE), 5 μg/ml bovine insulin, 0.18 μg/ml hydrocortisone, 5 μg/ml bovine transferrin and 0.2 ng/ml human epidermal growth factor.

NF-κB luciferase reporter assay

Primary keratinocytes seeded in 96-well plates were transfected with 0.1 μg pNF-κB-Luc reporter plasmid using Lipofectamine 2000 reagent. At 48 h post-transfection, cells were either left untreated or treated with 100 μg/ml TNF-α in the presence or absence of 1 ppb avenanthramides for 24 h. The cells were then lysed and luciferase readings were obtained using the Promega assay kit (Promega Corporation, Madison, WI, USA) according to the manufacturer's protocol.

Western blotting

Cells were washed with phosphate buffered saline and lysed with RIPA lysis buffer containing 65 mM Tris (pH 7.4), 150 mM NaCl, 1 mM EDTA (pH 8), 1% Nonidet P-40, 0.25% Sodium deoxycholate, 50 mM NaF, 1 mM Na_3VO_4, 1 mM PMSF and 1X protease inhibitor cocktail (Sigma). Lysates were centrifuged and total protein was estimated in the supernatants using the BCA Protein Assay Kit according to manufacturer's instructions (Pierce Biotechnology, Rockford, IL, USA). Protein (20 μg) was loaded on SDS-PAGE followed by immunoblotting with the specific antibodies and detection using the ECL chemiluminescence detection system (Amersham Life Sciences; Arlington heights, IL, USA).

Measurement of cytokine release

Primary human keratinocytes were seeded into 96-well plates at 15,000 cells per well and incubated at 37°C and 5% CO_2 for 24 h. Cells were left untreated or treated with 100 ng/ml TNF-α in the presence or absence of 1 ppb avenanthramides or 10 μM BAY 11-7085 for additional 24 h. IL-8 levels were analyzed in the supernatants using immunoassay multiplex kit (Upstate Biotechnology, Charlottesville, VA, USA) on a Luminex L100 (Luminex Corporation, Austin, TX, USA). Results were calculated using Graphpad Prism (GraphPad Software, San Diego, CA, USA).

Oxazolone-induced ear edema (contact hypersensitivity)

To assess the potential for avenanthramides to inhibit contact hypersensitivity responses, ICR mice were sensitized with 3% oxazolone as previously described [18]. Five days later they were challenged with oxazolone (2%) in acetone, administered to the dorsal left ear (20 μl), with the right ear

remaining untreated. One hour after the challenge 2 or 3 ppm avenanthramides in a 70% EtOH/30% propylene glycol vehicle or vehicle alone were applied to the dorsal left ear (20 µl) with the right ear untreated ($N = 7$ per group). Maximum response of this model is seen at 24 h. The percentage of inhibition was calculated by comparing the difference in ear weight between vehicle and avenanthramide-treated mice.

Resiniferatoxin-induced ear edema (neurogenic dermatitis)

Neurogenic inflammation was induced in ICR mice by topical application of 0.05% Resiniferatoxin (RTX) as previously described [18]. Immediately following RTX treatment, avenanthramides at a concentration of 2–3 ppm in a 70% EtOH/30% propylene glycol vehicle were applied (20 µl) to the dorsal left ear while the right ear was untreated ($N = 10$ per group). Maximum response in this model is seen at 30 min. The percentage of inhibition was calculated by comparing the difference in ear weight between vehicle and avenanthramide-treated mice.

Induced itch response

An itch-associated response was induced by intradermal injection of compound 48/80 in ICR mice, and scratching determined based on a modification of Liebel et al. [18]. Mice were individually housed in a plastic cage for at least 1 h before the experiment for acclimation. Mice were pretreated for 30 min with topical application of vehicle control, or 3 ppm avenanthramide prepared in 100% ethanol, to an area of the back that had been shaved 1 day prior to the experiment. Compound 48/80 was prepared in sterile physiological saline then 50 µL of a 1 µg/µL solution was injected into the interscapular part of the back and the number of scratches elicited during the 30-min period after injection was determined by visual observation.

Results

Avenanthramides regulate NF-κB signaling and IL-8 production in keratinocytes

We first looked at TNF-α induced inhibition of nuclear factor kappa B-α (IκB-α) degradation in control and avenanthramide treated cells. TNF-α treatment alone, induced degradation of IκB-α which was evident at 15 and 30 min. However, in cells that were pretreated with avenanthramides, no degradation of IκB-α was observed (Fig. 1a). The blot was probed with tubulin antibody to account for equal protein loading (Fig. 1a). This result coincided well with decreased phosphorylated p65 NF-κB levels in avenanthramide treated cells compared to control cells 15 and 30 min post-TNF-α stimulation (Fig. 1b). The same blot was blotted with the p65 antibody to show equal protein in each well (Fig. 1b). To further confirm the above results we assessed the role of avenanthramides on TNF-α dependent NF-κB luciferase reporter activity. TNF-α stimulated keratinocyte cells transfected with NF-κB luciferase vector showed a ninefold increase in NF-κB activity over control cells. Cells treated with avenanthramides showed a 1.7-fold inhibition of TNF-α induced NF-κB activity, which was statistically significant ($P < 0.05$) compared to TNF-α alone treated cells (Fig. 2a). BAY 11-7085, an NF-κB inhibitor was used as a positive control.

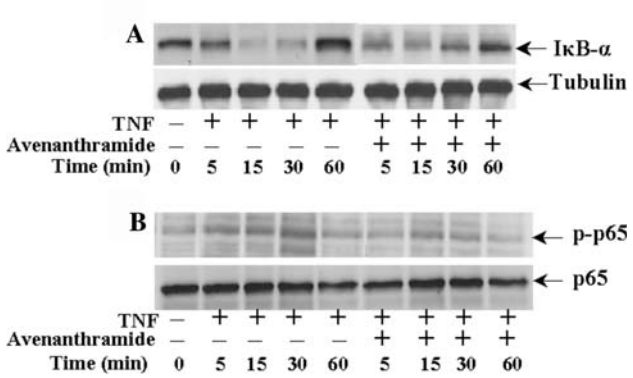

Fig. 1 Avenanthramides regulate NF-κB signaling in keratinocytes. **a** Primary keratinocytes were grown in six-well dishes and treated with 20 ng/ml TNF-α for the indicated times in the absence or presence of 1 ppb avenanthramides. Cells were lyzed in RIPA buffer and whole cell extracts (20 µg protein) were subjected to SDS/PAGE followed by blotting with IκB-α antibody and tubulin antibody. **b** Whole cell extracts (20 µg protein) of keratinocytes were subjected to SDS/PAGE followed by blotting with phospho-p65 and p65 antibodies

Since many of the pro-inflammatory cytokines, such as IL-8, are transcriptionally regulated by NF-κB, we next assessed the effect of avenanthramides on IL-8 production from keratinocytes. TNF-α induced IL-8 release from keratinocytes was inhibited by 1.4-fold in the presence of avenanthramides, indicating a statistically significant ($P < 0.001$) reduction in IL-8 release over TNF-α alone treated cells. BAY 11-7085, an NF-κB inhibitor completely inhibited IL-8 production (Fig. 2b).

Avenanthramides suppress contact hypersensitivity, neurogenic inflammation and itch responses

Exposure to oxazolone induces an immune-mediated allergic response (contact hypersensitivity) [33]. Topical treatment with avenanthramides significantly inhibited contact hypersensitivity in a dose dependent manner (Fig. 3a). The mean ear weight in oxazolone-challenged mice treated with 2 or 3 ppm avenanthramides were 6.24 ± 0.94 and

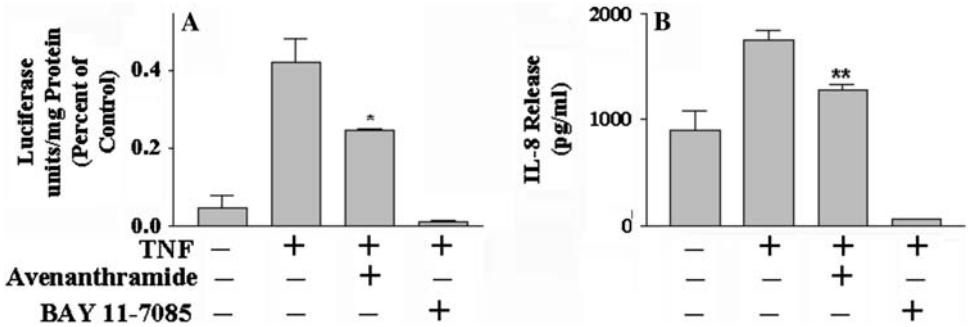

Fig. 2 Avenanthramides regulate NF-κB activity in keratinocytes. **a** Human primary adult epidermal keratinocytes were transfected with pNF-κB-Luc reporter plasmid. Cells were either left untreated or treated with 100 ng/ml TNF-α in the absence or presence of 1 ppb avenanthramides for 24 h. Samples treated with the NF-κB inhibitor BAY11-7082 were pretreated with the inhibitor for 30 min. Luciferase assay was performed as described in the "Materials and methods" section and the values were normalized to total protein in each well. Results represent mean ± SD from three different experiments. $*P < 0.05$ compared with keratinocyte cells treated with TNF-α alone. **b** Human primary epidermal keratinocyte cells were either left untreated or treated with 100 ng/ml TNF-α in the absence or presence of 1 ppb avenanthramides. Respective samples were pre-treated with the NF-κB inhibitor BAY11-7082 for 30 min. After 24 h supernatants were assessed for IL-8 levels by ELISA. $**P < 0.001$ compared with keratinocyte cells treated with TNF-α alone

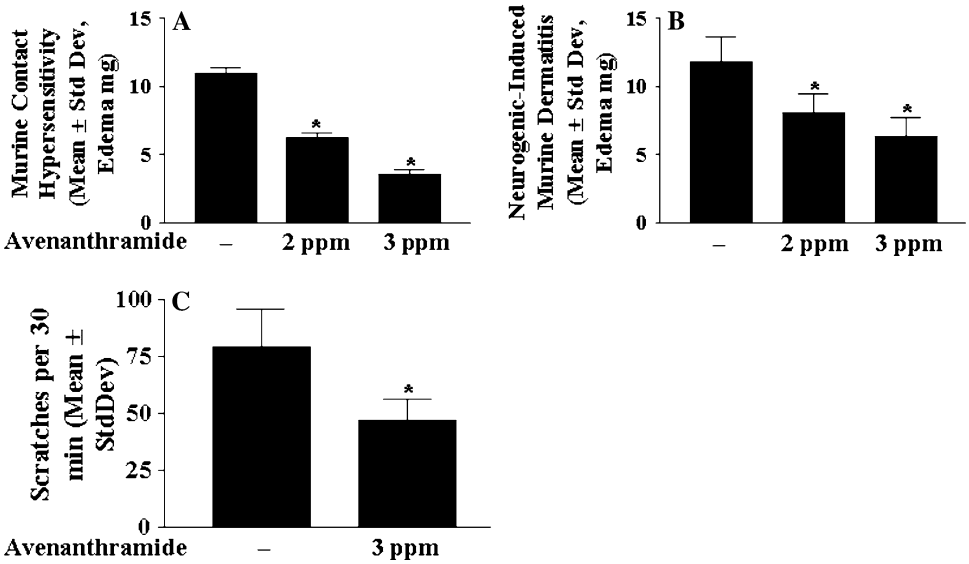

Fig. 3 Reduction of contact hypersensitivity, neurogenic inflammation and itch by topical application of avenanthramides. **a** CD-1 mice were sensitized to oxazolone and 5 days later challenged with oxazolone applied to the right ear; the left remained untreated ($N = 7$ per group). One hour after application of oxazolone (1 μg/ear), avenanthramides was applied to the oxazolone-treated ear. The results shown are mean ± SD. $*P < 0.05$ compared to oxazolone plus vehicle treated group. **b** CD-1 mice were treated with resiniferatoxin (*RTX*) applied to the right ear; the left remained untreated. Immediately after application of RTX (10 μg/ear), avenanthramides was applied to the RTX-treated ear ($N = 7$ per group). $*P < 0.05$ compared to RTX plus vehicle treated group. **c** Itch was induced by intradermal injection of compound 48/80 and scratching visually recorded. Avenanthramides (3 ppm) or ethanol vehicle were applied 30 min prior to compound 48/80 injection. The results shown are mean ± SD. $*P < 0.05$ compared to compound 48/80 plus vehicle treated group

3.58 ± 0.92 mg, respectively, compared with 10.93 ± 1.22 mg for oxazolone plus vehicle treated animals. This represented a statistically significant ($P < 0.05$) 42.89 and a 67.20% reduction in edema for the 2 or 3 ppm avenanthramide treated groups, respectively. Hydrocortisone (0.1%), the positive control in this model, reduced inflammation by 82.65%.

Topical administration of avenanthramides were also found to inhibit neurogenic inflammation. Resiniferatoxin (RTX) is a potent analog of capsaicin that activates the small diameter sensory neurons resulting in the induction of neurogenic inflammation and can be useful for the assessment of agents that may block neurogenic inflammation [31]. Topical application of 2 or 3 ppm of avenanthramides significantly ($P < 0.05$) reduced RTX-induced ear edema by 31.58 and 46.09%, respectively. Menthol (1.0%), the positive control in this model, reduced inflammation by 46.96%.

Since itch is a sensation that promotes the desire to scratch the stimulated area, scratching can be used as an objective measure of the degree of itching. Compound 48/80 induces histamine release from mast cells resulting in itch sensations [16] and administration of compound 48/80 has been shown to elicit pruritogenic (itch) responses in humans [27]. In the itch model, vehicle-treated animals scratched a mean of 79.2 ± 16.6 times per 30 min, while animals treated with 3 ppm avenanthramides scratched a mean of 47.0 ± 9.6 times per 30 min (Fig. 3c). This represented a statistically significant ($P < 0.05$) reduction in scratching in avenanthramide-treated animals by 40.7% compared to vehicle treated animals.

Discussion

For dermatologic applications, colloidal oatmeal is widely used as topical treatment for skin conditions such as atopic dermatitis and eczema, however the phytochemicals that mediate the anti-inflammatory and anti-itch activity of oats have not been identified. In our study we found that avenanthramides inhibited IκB-α degradation (Fig. 1a), activation of NF-κB p65 (Fig. 1b) and NF-κB luciferase activity (Fig. 2a) in keratinocytes. NF-κB is an important regulator of expression of many pro-inflammatory proteins. NF-κB proteins are sequestered in the cytoplasm bound to inhibitory proteins referred to as IκB in majority of cells. Exposure of cells to extracellular stimuli such as TNF-α leads to the activation of the IκB kinase (IKK) complex resulting in the phosphorylation and ubiquitination of the IκB proteins and their proteosome mediated degradation [1, 3, 5, 21]. Once IκB is degraded NF-κB subunits (comprising of p65, p50 and relA) are free to translocate to the nucleus and turn on gene transcription. Avenanthramides were also found to inhibit the phorbal ester induced NF-κB luciferase activity in keratinocytes (data not shown), suggesting that the inhibition of NF-κB activity by avenanthramides is not specific to TNF-α activation alone. To confirm that NF-κB inhibition by avenanthramides resulted in a decreased biological response, we looked at the effect of avenanthramides on release of the NF-κB dependent cytokine, IL-8, from keratinocytes. We found that avenanthramides inhibited IL-8 production, thus demonstrating that avenanthramides exert anti-inflammatory effects in these cells by inhibiting NF-κB signaling. These results are consistent with the recent work of Guo and co-workers [13] that found that synthetic avenanthramides reduce the stimulated production of pro-inflammatory cytokines from endothelial cells by inhibiting NF-κB activation and established that synthetic avenanthramides have activity compared to avenanthramides directly isolated from oats.

We next addressed whether topical application of avenanthramides would result in a reduction of inflammation. Topical application of 2–3 ppm of avenanthramides were found to significantly reduce the inflammatory response observed in the oxazolone model of contact hypersensitivity (Fig. 3a). Presumably the inhibition of cytokine release by avenanthramides mediates this decrease in skin inflammation. Topically applied avenanthramides also were found to significantly inhibit neurogenic inflammation (Fig. 3b), thus suggesting these oat proteins may have putative anti-itch activity. The release of neuropeptides, such as Substance P and calcitonin gene-related peptide, from peripheral terminals of unmyelinated small diameter sensory neurons, C-fibers, present in the skin act on peripheral blood vessels and immune cells producing an inflammatory response (i.e. neurogenic inflammation) that is characterized by erythema, edema, warmth and hypersensitivity [26]. Since pruritus is initiated by the release of these same neuropeptides from C-fibers, triggering nociceptive responses (itching, stinging, pain) [29], we next examined the effect of avenanthramides of itch responses. Using a murine model of induced itch we demonstrate that avenanthramides significantly reduced the scratching response by up to 40% compared to vehicle (Fig. 3c), which was comparable to the anti-itch effect produced by hydrocortisone. These results demonstrate that avenanthramides can modulate the nociceptive responses that occur during pruritic skin diseases.

Clinically the topical application of oat containing preparations are used for a variety of dermatologic conditions which are frequently characterized by itching; such as atopic dermatitis and eczema, [17]. Pruritus (itching) has been characterized as an unpleasant sensation which elicits the urge to scratch and can range in severity ranging from acute to intractable [4]. We demonstrated that avenanthramides inhibit the release of IL-8 (Fig. 1) indicating that these compounds are effective in inhibiting the release of inflammatory cytokines that have been shown to be elevated in pruritic skin diseases [19] and which may contribute to the itch sensations. In addition, the vicious itch-scratch cycle can result in disrupted skin integrity and subsequent decreased barrier resistance to infections [29], the anti-inflammatory activity of avenanthramides may reduce the scratching-induced secondary inflammation that can occur in atopic dermatitis and eczema, preventing the disrupted skin barrier function. Interestingly avenanthramides have a chemical structure similar to the drug Tranilast [*N*-(3′4′-dimethoxycinnamoyl)anthranilic acid] [13], which has anti-histamine activity, thus the anti-itch activity of avenanthramides may be related to the inhibition of histamine signaling. Taken together, these results demonstrate that topically applied avenanthramides were highly effective in reducing inflammation and itch responses at very

low levels (1–3 ppm), and thus likely represent the active phytochemicals present in oats for dermatologic applications.

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