Research article

Avenanthramides as lipoxygenase inhibitors

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ABSTRACT

Avenanthramides (AVAs) present in oats are amides of anthranilic and cinnamic acids. AVAs are potent antioxidants and have anti-inflammatory properties. There are various potential mechanisms for their anti-inflammatory effects, including inhibition of lipoxygenases (LOX), which catalyse oxygenation of polyunsaturated fatty acids into potent signal molecules involved in inflammatory processes. In this study, AVAs were screened for LOX inhibition in vitro and structure-activity relationships were examined. Twelve different AVAs at 0.6 mM were tested as LOX inhibitors. The corresponding free cinnamic acids, the AVA analogue Tranilast® and the known LOX inhibitor tran-resveratrol were included for comparison. It was found that AVAs comprising caffeic or sinapic acid exhibited significant lipoxygenase inhibition (60–90%) (P < 0.05), whereas low or no inhibition was observed with AVAs containing p-coumaric or ferulic acid. No difference in inhibition was seen on comparing AVAs with their free corresponding cinnamic acids, which implies that the anthranilic acid part of the avenanthamide molecule does not affect inhibition. Tran-resveratrol showed inhibition, whereas no inhibition was seen for Tranilast® at the concentrations used in this study. This study suggests that avenanthramides comprising caffeic acid or sinapic acid partly exert their antioxidant and anti-inflammatory effects via lipoxygenase inhibition.

1. Introduction

Lipid oxidation is an important process in many different biological systems. In a food context, lipid oxidation is one of the major causes of food deterioration, as it may lead to off-flavours, changes in colour and texture and also decreased nutritional value of food products (Croguennec, 2016). Lipid oxidation can proceed in either a non-enzymatic or an enzymatic fashion. Lipoxygenases (LOX) constitute a family of non-haem iron-containing enzymes that catalyse oxygenation of fatty acids and are widely distributed in plants and animals (Hildebrand, 1989; Kuhn et al., 2015; Horn et al., 2015). In plants, the substrate is mainly linoleic acid (LA) (C18:2, n-6) and α-linolenic acid (ALA) (C18:3, n-3), whereas in mammals it is arachidonic acid (AA) (C20:4, n-6). In mammals vegetable LA can be transformed to AA though enzyme mediated elongation and desaturation reactions. The same reactions also transform ALA to eicosapentaenoic acid (EPA, C20:5, n-3) and docosahexaenoic acid (DHA, C22:6, n-3). Lipid oxidation can be a problem in living systems, by altering the function of membranes and lipoprotein particles (Kuhn et al., 2015). In mammalian cells, LOX catalyse the initial step in the conversion of AA to the hydroperoxide, 5-hydroperoxy-6,8,11,14-eicostetraenoic acid, and are thereby key enzymes in the biosynthesis of a variety of bio-regulatory compounds such as leukotrienes (Pergola and Werz, 2010; Hägström and Funk, 2011; Rådmark et al., 2015). Leukotrienes are considered to be potent mediators of pro-inflammatory reactions. LOX enzymes are also associated to biosynthesis of compounds which may promote termination of acute inflammation reactions, and thereby function as anti-inflammatory agents. Such compounds are for example lipoxins, which are biosynthesised via oxygenation of AA, and resolvins, biosynthesised though oxygenation of the ω-3 fatty acids EPA and DHA (Pirault and Bäck, 2018; Becchi et al., 2019; Kuhn et al., 2015; Rådmark et al., 2015). Acute inflammation is a protective process. However, overbalance of pro-inflammatory vs anti-inflammatory agents over time may result in a variety of chronic inflammatory diseases, such as arthritis, bronchial asthma, and cardiovascular diseases (Yoon and Baek, 2005; Pergola and Werz, 2010; Chen, 2011; Hägström and Funk, 2011; Kuhn et al., 2015; Bruno et al., 2018). Therefore, inhibition of the pro-inflammatory LOX pathway is suggested to be interesting for prevention of these diseases. Many of the LOX inhibitors are found among the class of phenolic compounds, which have radical scavenging and/or iron chelating properties,
and among fatty acid analogues (Yoon and Baek, 2005; Schneider and Bucar, 2005a, 2005b; Pergola and Werz, 2010; Chen, 2011).

Avenanthramides (AVAs) belong to a group of phenols comprising anthranilic and cinnamic acid derivatives (Figure 1a; Table 1). Among cereals, AVAs are found only in oats and so far 15 compounds have been identified (Dimberg et al., 1993; Matsukawa et al., 2000; Bratt et al., 2003; Collins, 2011; Ishihara et al., 2014; Readelli et al., 2015; Pridal et al., 2018; de Bruijn et al., 2019). The three most abundant AVAs in oat groats are 2p, 2f and 2c, the 2 indicating 5-hydroxyanthranilic acid (as opposed to 1 for anthranilic acid, 3 for 5-hydroxy-4-methoxyanthranilic acid, 4 for 4-hydroxy anthranilic acids and 5 for 4,5-dihydroxyanthranilic acid), and the p, f and c indicating the cinnamic acids p-coumaric, ferulic and caffeic acid, respectively (Bratt et al., 2003; Fagerlund et al., 2009; Dimberg and Jastrebova, 2009; Ishihara et al., 2014; Readelli et al., 2015; de Bruijn et al., 2019). Other AVAs with cinnamic acids replaced by the corresponding avenalumic acids (5-phenyl-penta-2,4 dienoic) are also present in oats (Dimberg and Jastrebova, 2009; Collins, 2011; Ishihara et al., 2014; Pridal et al., 2018; de Bruijn et al., 2019). Sinapic acid (α) is found in oats, but no AVAs derived from this acid have been found in oat plants (Bratt et al., 2003; Collins, 2011).

![Figure 1. Structures of compounds used in the experiments: a) avenanthramides (1s, 2s and 3s are not found in oats), Tranilast®, and cinnamic acids (see Table 1 for the substitution pattern of the molecular skeletons) and b) trans-resveratrol.](image-url)

Consumption of oats has been linked to a decreased risk of several chronic diseases and it has been suggested that AVAs contribute to the protective effects (Meydani, 2009; Tripathi et al., 2018). In *in vitro* studies, AVAs have been characterised as antioxidants with a clear structure-activity relationship (Dimberg et al., 1993; Bratt et al., 2003; Fagerlund et al., 2009; Lee-Manion et al., 2009; Ishihara et al., 2014). They have also been shown to be bioavailable (Zhang et al., 2017) and to exert antioxidant activity in vivo (Ji et al., 2003; Chen et al., 2004, 2007; Koenig et al., 2014). Furthermore, they have been found to exhibit anti-inflammatory, anti-proliferative and anti-itch activities in vitro and in vivo (Nie et al., 2006a, 2006b; Sur et al., 2008; Koenig et al., 2014; Reynertson et al., 2015; Hastings and Kenealey, 2017; Scarpa et al., 2018). In a food context, AVAs have been shown to be correlated to the fresh oat taste of oat products (Molteberg et al., 1996).

In this study it is hypothesized that AVAs partly protect oat foods from rancidity development through inhibition of LOX activity. Furthermore, a hypothesis is that AVAs may inhibit LOX and/or cyclooxygenase (COX-2) enzymes in mammals and thereby decrease the production of pro-inflammatory compounds, such as leukotrienes and prostaglandins. An AVA-enriched oat extract has been shown to inhibit cyclooxygenase (COX-2) activity and pro-inflammatory prostaglandin production from AA in mouse macrophages (Guo et al., 2010). Furthermore, a butanolic fraction of oat groats has been found to have anti-platelet activities mediated though inhibition of the COX and LOX pathways (Ahmed et al., 2013). The authors of the latter study did not speculate about the possible compounds involved, but a high amount of AVAs is probably present in a butanol extract, since methanol and ethanol are good extracting solvents for AVAs (Dimberg and Jastrebova, 2009).

The aim of the present work was to investigate whether pure AVAs and their corresponding free cinnamic acids (Figure 1a; Table 1), have LOX inhibitor activity in *vivo*. A further aim was to establish a structure-inhibition activity relationship. Trans-resveratrol (Fig. 1b), a phenolic stilbene known to possess LOX inhibitor activity (Fan and Mattheis, 2001; Chatterjee et al., 2011), was used as a positive control. Tranilast® (Figure 1a; Table 1), a known non-phenolic drug with anti-inflammatory properties (Pae et al., 2008; Darakhshan and Pour, 2015) and with remarkable chemical similarities to the AVAs was used as a negative control (Komatsu et al., 1988).

2. Materials and methods

2.1. Chemicals

Lipoxygenase, LOX 1 from soybean, (EC 1.13.11.12), was purchased from SIGMA Chemicals Co. (St. Louis, MO, USA), linoleic acid from Calbiochem® (U.S and Canada), sinapic acid from Fluka Chemie AG (Buchs SG, Switzerland) and ferulic-, caffeic- and p-coumaric acid from SIGMA Chemicals Co. (St. Louis, MO, USA). All AVAs were synthesised according to Bratt et al. (2003) (1- and 2-series) or Fagerlund et al. (2009) (3-series). All other chemicals used were *pro analysi* and were used without further purification.

2.2. HPLC analysis

Reverse-phase high performance liquid chromatography (RP-HPLC) analysis was performed with an HP series 1100 instrument (Hewlett Packard, Waldbronn, Germany) equipped with diode array detector (DAD) and a HP ODS Hypersil column (5 μm, 125 mm × 4 mm). The isocratic mobile phase was acetonitrile:0.01M phosphate buffer (pH 2.8) containing 5% acetonitrile (70:30). Sample size injected was 10 μL and the flow rate was 1 mL/min. Products of LOX activity were detected at 234 nm (Villafuerte Romero and Barrett, 1997). Peaks were identified from retention times (Figure 2) and UV-spectra, and were manually integrated using the software HP ChemStation Version 05.01.
2.3. Preparation of solutions

Enzyme solution was prepared by thoroughly mixing 4 μL enzyme with 20 mL 0.1 M borate buffer (Na3(BO)3/HCl), pH 9. Substrate solution was prepared by dispersing 15 μL linoleic acid in 60 mL 0.1 M borate buffer (pH 9) containing 15 μL Tween 20, shaking thoroughly and then sonicating for 1 min. AVAs, Tranilast®, trans-resveratrol and the cinnamic acid derivatives were prepared as 9 mM stock-solutions in ethanol/borate buffer (15/85). All solutions were used promptly to avoid autoxidation and degradation of enzyme.

2.4. LOX assay

Enzyme solution (100 μL) was mixed with 200 μL of a stock-solution of the test compound and the mixture was incubated for 10 min. Then 2.7 mL of linoleic acid solution were added and the mixture was vortexed and incubated in a 30 °C water bath for 30 min. The enzymatic reaction was stopped by adding 100 μL of concentrated hydrochloric acid. The reaction mixture was extracted with 3.0 mL of ethyl acetate. A 2 mL sample of the organic phase was collected and evaporated to dryness in a centrifuge evaporator. The solid residue was dissolved in 200 μL of methanol and analysed by HPLC. As a control sample, ethanol/buffer solution without added test compound was used. In addition, a control in which hydrochloric acid was added to the enzyme solution prior to reaction mixture was extracted with 3.0 mL of ethyl acetate. A 2 mL sample of the organic phase was collected and evaporated to dryness in a centrifuge evaporator. The solid residue was dissolved in 200 μL of methanol and analysed by HPLC. As a control sample, ethanol/buffer solution without added test compound was used. In addition, a control in which hydrochloric acid was added to the enzyme solution prior to incubation with linoleic acid, expressed as area units. The inhibition was calculated as the enzyme activity difference between reaction with and without added test compound. Since the enzyme activity slightly differed between the experiments, inhibition was expressed as percentage of uninhibited sample within each experiment.

2.5. Statistics

Analysis of variance with Tukey’s pairwise comparison (α = 0.05) was conducted using the software Minitab release 11.12 (Minitab Inc., State College, PA). Each experiment (A-H) was run separately with three replicates of each compound (except for 2s in experiment G, which was run with two replicates). All comparisons were made within each experiment (A-H) since the conditions between experiments varied somewhat.

3. Results

The lipoxygenase activity expressed as the relative amount of conjugated dienes formed from linoleic acid in the presence of the test compounds is shown in Figure 3, where each letter (A-H) represents one experiment.

3.1. Structure-activity relationship of LOX inhibition

3.1.1. Influence of the anthranilic acid moiety

No significant difference in inhibition activity was found between the free cinnamic acids p-coumaric acid (p), ferulic acid (f), caffeic acid (c) and sinapic acid (s) and their corresponding AVAs (Figure 3, experiments A-D), except that s showed significantly higher inhibition than 3s. Moreover, no differences were found within the 1- or 2-series of AVAs (experiments A-D) except for 2f, which exerted slightly higher inhibition than 3f, and for 3s, which showed lower inhibition than 1s and 2s. Compared to controls, the p-serie inhibited the LOX enzyme 0–30% (experiment A), the f-serie 0–20% (experiment B), the c-serie 50–70%
(experiment C) and the s-serie 60–90% (experiment D). These results indicate that the anthranilic acid part of the avenanthramides was of minor importance for the inhibition.

3.1.2. Influence of the cinnamic acid moiety

Among the free cinnamic acids, caffeic (c) and sinapic (s) acids showed significant inhibition of LOX activity (60–90%) compared to the control, whereas p-coumaric (p) and ferulic (f) acids showed low or no inhibition (Figure 3, experiments A-D, E). The difference in inhibition between c and s was not significant (experiment E). A similar pattern was observed when the 1-series of AVAs was studied (experiment F), i.e. 1c and 1s significantly inhibited LOX, whereas 1p and 1f did not. Again, there was no significant difference between the inhibition of 1c and 1s. The experiment with the 2-series of avenanthramides showed that 2c and 2s, but also 2f, had significant inhibitory effects and that all were significantly different in their activity, following the order 2s > 2c > 2f (experiment G). The LOX activity was approximately 1.2 times higher in the sample with AVA 2p compared with the control (experiment G). However, this was not observed in experiment A. The 3-series could not be evaluated in this context, due to lack of material. However, from experiments A-D it was evident that 3c and 3s inhibited the LOX activity by 50–60% and 3p inhibited it by around 30%, whereas no inhibitory activity was found for 3f. This confirms that the cinnamic acid part of the AVAs, especially those containing caffeic and sinapic acids, was important for LOX inhibition.

3.1.3. Controls

Trans-resveratrol was an effective lipoxygenase inhibitor when present in the assay at a concentration of 0.60 mM, but Tranilast® was not (Figure 3, experiment H).

4. Discussion

Although it has been shown that different phenols have LOX-inhibiting activity, the mechanisms involved have not been fully identified. In the active form of LOX, there is a ferric ion (Fe³⁺) at the active site. When linoleic acid is oxidised, the electron from the hydrogen atom is transferred to Fe³⁺ and its proton to a proton acceptor. The Fe³⁺ ion is thus reduced to a ferrous ion (Fe²⁺), rendering the enzyme inactive. The linoleic acid radical formed is re-arranged to a conjugated diene radical, which reacts with oxygen to form a peroxy radical. The peroxy radical reacts further with a proton and the electron from Fe²⁺ to form a...
hydroperoxide, Fe$^{2+}$ is oxidised to Fe$^{3+}$, the enzyme is thereby re-activated and the reaction can re-start with another linoleic acid (Hildebrand, 1989; Häggström and Funk, 2011). The mechanism of LOX inhibition can be explained in several ways, e.g. the inhibitor may scavenge the linoleic acid radicals formed, it may chelate or reduce the Fe$^{3+}$ ion in the active site of the enzyme, or it may interact with the enzyme molecule.

Caffeic and sinapic acids and their corresponding AVAs were the most efficient inhibitors in the present study. These compounds are also strong antioxidants when tested in diphenylpicrylhydrazyl (DPPH) and non-enzymatic linoleic acid diene formation assays (Bratt et al., 2003; Fagerlund et al., 2009; Lee-Manion et al., 2009; Ishihara et al., 2014), both of which methods rely on a radical scavenging mechanism. The stronger antioxidation activity of c and s derivatives found was expected, as they are able to stabilise the phenolic radical formed better than p and f derivatives. However, if the enzymatic inhibition shown in the present study had been caused solely by radical scavenging, the 3-series of AVAs would have been expected to be more active than the 2-series, which in turn would have been more active than the 1-series. This was not the case. Instead, it was found that there was no significant difference between the free cinnamic acids and their corresponding avenanthramides from the 1-, 2- and 3-series (Figure 3, experiments A-D). We therefore

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**Figure 3.** Products formed after lipoxygenase (LOX) activity on linoleic acid in the presence of avenanthramides, their corresponding cinnamic acids, Tranilast$^\text{®}$ or trans-resveratrol at 0.6 mM, expressed as percentage of controls (uninhibited samples). Each capital letter (A–H) represents one experiment. Error bars are given as coefficient of variation (CV) (except for 2s in experiment G, which is given as the difference between the two replicates). Different superscript letters within each experiment A–H indicate significant differences (p < 0.05) between the compounds tested.
suggestion that chelation of the Fe$^{3+}$ iron within the active site of the enzyme is important. However, it seems that a phenolic structure is also important, since the non-phenolic molecule Tranilast®, with the same basic skeleton as the AVAs (Figure 1 a; Table 1), did not have any inhibitory properties under the test conditions. Tranilast® is an anti-inflammatory substance (Komatsu et al., 1988; Pae et al., 2008; Darakhshan and Pour, 2015), but the anti-inflammatory activity appears to be dependent on other mechanisms rather than through LOX inhibition. Other studies have also demonstrated that cinnamic acid analogues lacking the redox-active phenolic hydroxyl groups lose all LOX inhibitory activity and that radical scavenging is not sufficient to ensure efficient LOX inhibition (Doiron et al., 2017; Touabia et al., 2018).

We could not determine whether the inhibition observed in the present study was caused by an interaction between the phenolic compounds and the enzyme, since the initial velocity of product formation was not monitored. However, it is unlikely that the active compounds acted as competitive inhibitors, since their structures are very different from that of the substrate, i.e. linoleic acid. Nevertheless, other interactions between inhibitors and the enzyme may occur, as other studies have shown that caffeic acid derivatives exert both non-competitive (Koshihara et al., 1984) and uncompetitive (Sudfina et al., 1993) inhibition. These compounds have also been reported to inhibit the enzyme by chelating iron ions, thereby preventing catalysis (Young, 1999).

We recognize that high concentrations of AVAs have been used in our in vitro experiments. AVAs are bioavailable (Chen et al., 2004, 2007; Zhang et al., 2017), but whether dietary AVAs at intake levels normally achieved through consumption of oat products exert LOX inhibitory activity in vivo, and thereby inhibit production of pro-inflammatory compounds, remains to be elucidated. In this context it may also be of importance to emphasize that the lipid content in grains of various oat cultivars is comparably high (49–135 g kg$^{-1}$) and that LA and AIA comprise about 40% and 1%, respectively, of the fatty acids present (Bryngelsson et al., 2002; Sterna et al., 2016). Theoretically, this may imply that oat derived LA, as a precursor to AA, could adversely affect the inflammatory processes and thereby counteract the possible protective effect of the avenanthramides. However, studies performed on healthy humans consuming a Western diet, have failed to show that additional dietary intake of LA is positively associated with pro-inflammatory markers, such as e.g. interleukin-6 (IL-6), interleukin-1β (IL-1β), tumour necrosis factor (TNF-α) and c-reactive protein (CRP) in the plasma (Innes and Calder, 2018; Fritsche, 2015).

In conclusion, AVAs have been shown to possess anti-inflammatory properties and the present study provides in vitro findings suggesting that this could be due to inhibition of LOX activity. These findings, together with findings from previous studies on antioxidant activity (Dimberg et al., 1993; Pratt et al., 2003; Fagerlund et al., 2009; Lee-Manion et al., 2009; Ishihara et al., 2014), may indicate that oat AVAs (especially the c-derivatives, as s-derivatives are not found in oats) can protect oat foods from rancidity development and contribute to anti-inflammatory effects in mammals. Further studies on foods and in vivo studies in mammarys are needed to confirm this.

**Declarations**

**Author contribution statement**

Rikard Landberg: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Kerstin Sunnerheim: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Lena H. Dimberg: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.

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**Competing interest statement**

The authors declare no conflict of interest.

**Additional information**

No additional information is available for this paper.

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