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Acetaminophen inhibits cytochrome c redox cycling induced lipid peroxidation

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ABSTRACT

Cytochrome (cyt) c can uncouple from the respiratory chain following mitochondrial stress and catalyze lipid peroxidation. Accumulating evidence shows that this phenomenon impairs mitochondrial respiratory function and also initiates the apoptotic cascade. Therefore, under certain conditions a pharmacological approach that can inhibit cyt c catalyzed lipid peroxidation may be beneficial. We recently showed that acetaminophen (ApAP) at normal pharmacologic concentrations can prevent hemoprotein-catalyzed lipid peroxidation *in vitro* and *in vivo* by reducing ferryl heme to its ferric state. We report here, for the first time, that ApAP inhibits cytochrome c-catalyzed oxidation of unsaturated free fatty acids and also the mitochondrial phospholipid, cardiolipin. Using isolated mitochondria, we also showed that ApAP inhibits cardiolipin oxidation induced by the pro-apoptotic protein, tBid. We found that the IC_{50} of the inhibition of cardiolipin oxidation by ApAP is similar in both intact isolated mitochondria and cardiolipin liposomes, suggesting that ApAP penetrates well into the mitochondria. Together with our previous results, the findings presented herein suggest that ApAP is a pleiotropic inhibitor of peroxidase catalyzed lipid peroxidation. Our study also provides a potentially novel pharmacological approach for inhibiting the cascade of events that can result from redox cycling of cyt c.

1. Introduction

The normal function of cytochrome c (cyt c) is the transfer of electrons between the respiratory complexes III and IV in the mitochondria. However, cyt c also functions as a peroxidase. Acting as a peroxidase, cyt c catalyzes reduction of hydroperoxides, including H_2O_2, by a process that generates a radical that catalyzes lipid peroxidation [1–3].

This concept is derived from several observations starting in 1959 when Tappel and Zalkin were first to demonstrate that cytochrome c could catalyze peroxidation of unsaturated fatty acids [4]. This observation was later extended to the mitochondria when Scott and Hunter showed that generation of lipid peroxidation in the mitochondria was greatly dependent on cytochrome c [5], a finding extensively confirmed subsequently [6–14]. Cytochrome c catalyzed lipid peroxidation may be involved in many cellular processes ranging from phosphatidylserine externalization during apoptosis [15] to modification of mitochondrial function [16] and triggering cytochrome c release during apoptosis [15].

Acetaminophen (ApAP) is one of the most widely used analgesics. We and others have shown that it inhibits the prostaglandin H_2 synthase by reducing the protoporphyrin radical cation in the peroxidase active site of the enzyme, thereby blocking formation of the catalytic tyrosyl radical in the cyclooxygenase site [17,18]. We later showed that ApAP could similarly inhibit the peroxide-driven lipid peroxidation catalyzed by myoglobin and by hemoglobin [19] and presented the proof of concept that ApAP could be

Abbreviations: AA, arachidonic acid; ApAP, acetaminophen; CL, cardiolipin; cyt c, cytochrome c; ETC, electron transport chain; HPLC, high performance liquid chromatography; L_4CL, tetralinoleoyl cardiolipin; LC–MS, liquid chromatography–mass spectrometry; M_4CL, Tetra myristoyl CL; MOM, mitochondrial outer membrane; PGHS, prostaglandin H_2 synthase; POPC, 1-palmitoyl-2-oleoyl-3-phosphatidylcholine; SRM, selective reaction monitoring; TLC, thin layer chromatography; UPLC, ultra pressure liquid chromatography.

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used *in vivo* to protect the kidney from oxidative damage following rhabdomyolysis [19].

Herein we describe for the first time the ability of ApAP to inhibit peroxidation of unsaturated fatty acids catalyzed by cytochrome c *in vitro* using free arachidonic acid and tetralinoleoyl cardiolipin. Importantly, we show that ApAP can prevent cardiolipin oxidation in isolated mitochondria following activation of apoptosis by tBid.

2. Materials and methods

2.1. Reagents

Phospholipids, 1-palmitoyl-2-oleoyl-3-phosphatidylcholine (PO PC), tetralinoleoyl cardiolipin (L_4CL), tetramyristeoyl cardiolipin (M_4CL) were purchased from Avanti Polar Lipids (Alabaster, AL) and used without further purification. All other chemicals were purchased from Sigma–Aldrich Chemical Company (Milwaukee, WI). HPLC quality solvents, such as methanol, water, 2-propanol, and acetonitrile were purchased from either Fisher Chemical (Phillipsburg, NJ) or EM Science (Gibbstown, NJ).

2.2. Inhibition of cyt c induced oxidation of arachidonic acid by ApAP

Oxidation of arachidonic acid (AA) by cyt c and H_2O_2 was performed based on minor modification of the protocol used for myoglobin [19]. Briefly, cyt c (50 μM) was mixed with [^{14}C] AA (10 μM) and various concentrations of ApAP. The reaction was initiated with the addition of hydrogen peroxide (H_2O_2, 250 μM) and incubated at 37 °C for 3 h. Oxidation products were quantified as previously described [19]. Control experiments for each drug concentration were also performed in which cyt c was omitted. The radioactivity associated with products of oxidation of [^{14}C] AA incubated without cyt c (background oxidation) was subtracted from each value obtained in presence of cyt c in the same conditions. The IC_{50}'s for ApAP were calculated using the logit method. Data are presented as the mean ± SEM.

2.3. Oxidation of L_4CL in liposome by cyt c and hydrogen peroxide

Oxidation of L_4CL in liposomes by cyt c and H_2O_2 was carried out based on a published protocol [20]. CL and POPC stored in chloroform were mixed in a glass vial and the solvent was removed by a flow of nitrogen. PBS (50 mM, pH 7.4) with 100 μM DTPA was added to achieve final concentrations of 50 μM CL and 200 μM POPC. Then, the lipid mixture was vortexed and sonicated for 1 min under nitrogen. Cyt c (5 μM final concentration) and various concentrations of ApAP ranging from 0 to 500 μM were added, and the reaction was initiated by adding H_2O_2 (100 μM final concentration). After 30 min at 37 °C, the reaction was stopped by adding 2 U/ml catalase. 0.75% NaCl was added and the oxidation mixture was extracted with chloroform and methanol (2:1, v:v) containing 0.1 mM butyrated hydroxytoluene and 0.1 mM triphenylphosphine and 2.5 μg tetramyristeoylcardiolipin (M_4CL) as internal standard. The separated organic phase was evaporated, resuspended in methanol:acetonitrile:H_2O (60:20:20, v/v/v) and stored at −80 °C until analysis by LC–MS as described below.

2.4. ApAP inhibits CL oxidation in isolated mitochondria

The efficacy of ApAP to inhibit CL oxidation in isolated mitochondria was determined as described. Mouse liver mitochondria were isolated as previously described [21]. Fifteen microgram of mitochondria were pre-incubated with 0–400 μM ApAP for 10 min. Recombinant tBid (10 ng) was added to the mitochondria and the samples were incubated for 30 min at room temperature. Mitochondria were pelleted by centrifugation at 8000 rpm for 10 min at 4 °C. The oxidation products of CL (OxCL) in the pellets were processed as described above for the liposomes and analyzed by LC–MS as described below.

2.5. Quantification of oxidation products of CL by liquid chromatography–mass spectrometry (LC–MS)

Analysis of oxidation products of CL by LC–MS was carried out as described previously [22]. The extracted lipid fraction was separated online by UPLC using a Waters Acquity UPLC system (Waters Corp., Milford, MA). Mass spectrometry analysis was performed on a Thermo Quantum Ultra triple quadrupole mass spectrometer (Thermo Scientific Inc., San Jose, CA, USA). The mass spectrometer was operated in the negative ion mode using selective reaction monitoring (SRM). Nitrogen was used as the sheath gas at 38 p.s.i. The capillary temperature was 350 °C. The spray voltage was 4.5 kV, and the tube lens voltage was 100 V. Data acquisition and analysis were performed using Xcalibur software, version 2.0. The molecular ion corresponding to the doubly charged monohydroxyL_4CL ([L_4CL-OH − 2H]$^{2-}$; m/z = 731.6) was monitored as a major species of OxCL. The following transitions were monitored in SRM: M_4CL, m/z 619.6–227.2; L4CL, m/z 723.6–279.2; CL-OH, m/z 731.6–279.2, and 731.6–295.2.

The area under the curve (AUC) for oxidized cardiolipins (OxCL), M_4CL and L_4CL were determined and the AUC of OxCL and L_4CL in each sample were normalized to the M_4CL AUC. The corrected values were used to calculate the ratio OxCL over total CL and were expressed as percent of total CL. Data are presented as the mean ± SEM.

3. Results

3.1. Acetaminophen inhibits cyt c redox cycling induced oxidation of arachidonic acid (AA)

We studied the ability of ApAP to inhibit peroxidation of unsaturated fatty acids catalyzed by cytochrome c *in vitro* using radiolabeled arachidonic acid. The experiments were performed in the presence of 250 μM H_2O_2 for three hours according to preliminary experiments showing that in these conditions all the substrate was not oxidized at the end of the reaction. Our results show that ApAP inhibits lipid peroxidation catalyzed by cyt c with an IC_{50} of 91 ± 47 μM (n = 5) (Fig. 1). The IC_{50} of ApAP in these experimental conditions is well within its normal therapeutic range in humans (67–200 μM).

3.2. Acetaminophen prevents cyt c mediated cardiolipin oxidation in liposomes

Several studies have established that association of cyt c with several families of lipids enhances the ability of cyt c to catalyze lipid peroxidation [1,11,12,15]. In more recent work, evidence has emerged for a preponderant role of cardiolipin (CL), a class of lipid primarily associated with the mitochondria where cyt c is located. Tetralinoleoyl CL (L_4CL) is the major CL in mammalian cells and oxidation of L_4CL leads to the formation of lipid hydroperoxides as the primary oxidation products [22]. We developed an LC–MS method to quantify the L_4CL oxidation products. In this method, the CL-OOHs are reduced by triphenylphosphine and the resulting CL-OHs are monitored by selective reaction monitoring. Tetramyristoyl CL (M_4CL) is used as an internal standard (Fig. 2A). We found that ApAP potently inhibited cyt c catalyzed oxidation of L_4CL (Fig. 2B) with an IC_{50} of 22.8 ± 7.6 μM (n = 6). It is noteworthy that

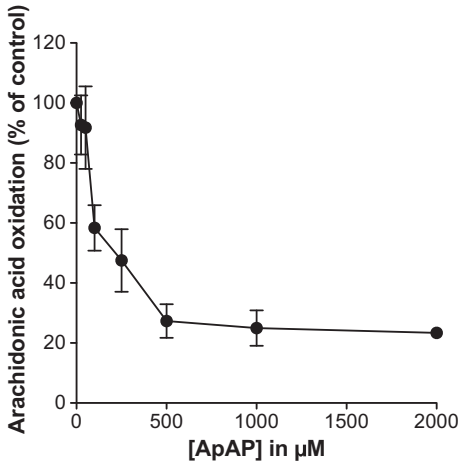

Fig. 1. ApAP inhibits cyt c induced oxidation of arachidonic acid (AA). [^{14}C] AA was incubated with cyt c and various concentrations of ApAP as described in the methods section. The residual AA and the oxidized products were extracted and analyzed as described previously [19]. The oxidation is represented as the percentage of AA oxidized by cyt c at 3 hours versus the control in which no ApAP is added. Each data point represents the mean ± S.E.M. (n = 4).

we also found that the ability of ApAP to inhibit cyt c mediated CL oxidation is much greater than its ability to inhibit cyt c mediated oxidation of AA (Fig. 1), which is consistent with the observation that binding to CL enhances cyt c ability to catalyze lipid peroxidation [11].

3.3. Acetaminophen inhibits cyt c mediated cardiolipin oxidation in mitochondria

Emerging evidence suggests that CL plays an active role in mitochondrial function, including the regulation of mitochondrial outer membrane (MOM), mobilization of cyt c, and anchoring of caspase-8 to mitochondria during death receptor-induced apoptosis [23]. Therefore, we investigated whether ApAP inhibits oxidation of CL in mitochondria isolated from mouse liver. We used tBid, a pro-apoptotic Bcl2 family member, to activate the mitochondria because of the evidence showing that tBid causes the remodeling of mitochondrial cristae and CL oxidation [24]. Our data shows that ApAP dose-dependently inhibits mitochondrial CL oxidation (Fig. 3) with an IC_{50} of 32.5 ± 5.5 μM (n = 6). Interestingly, the potency of ApAP to inhibit CL oxidation in isolated mitochondria is not significantly different from that obtained with liposomes (Mann Whitney, p = 0.20) (Fig. 2B), suggesting that ApAP exhibits high penetrance into mitochondria.

4. Discussion

Recently we have shown that ApAP can prevent hemoprotein-catalyzed lipid peroxidation *in vitro* by reducing ferryl heme to its ferric state and that ApAP is highly protective against myoglobin redox cycling induced renal injury in an animal model of rhabdomyolysis-induced renal failure [19]. We have extended this discovery to the peroxidase activity of cyt c and obtained evidence indicating that ApAP is also capable of inhibiting cyt c redox cycling-induced lipid peroxidation.

As a heme protein, cyt c can function as a peroxidase. Its ability to catalyze oxidation of unsaturated fatty acids is well documented and it is thought to be contributing to several cellular dysfunctions following oxidative stress [1,4,5,15,16,20]. Using the same assay that we developed for myoglobin and hemoglobin [19], we showed that ApAP was able to inhibit lipid peroxidation catalyzed by H_2O_2-activated cyt c *in vitro* at concentrations that are within the therapeutic range in humans.

Cyt c-dependent lipid peroxidation is known to be greatly increased when the protein associates with esterified lipids such as cardiolipin, the major lipid present in the mitochondria [11]. It is thought that binding of cyt c to CL unfolds the protein and facilitates the opening of the heme catalytic site to peroxides [25,26]. Partially unfolded cyt c in the complex with CL exerts an almost 100-fold higher catalytic activity as a peroxidase in the presence of H_2O_2 than the native protein [27]. Using liposomes of cardiolipin, an established model for investigating this process, we show that ApAP inhibits oxidation of the polyunsaturated fatty acid-containing CL, L_4CL, with an IC_{50} 4-fold lower than for free arachidonic acid.

CLs are predominantly located in the inner mitochondrial membranes and intimately interact with the electron transport chain (ETC) complexes involved in oxidative phosphorylation [28,29]. Furthermore, CL is also associated with members of the apoptotic machinery including cyt c, Bid, and caspase 8 [30,31]. Although

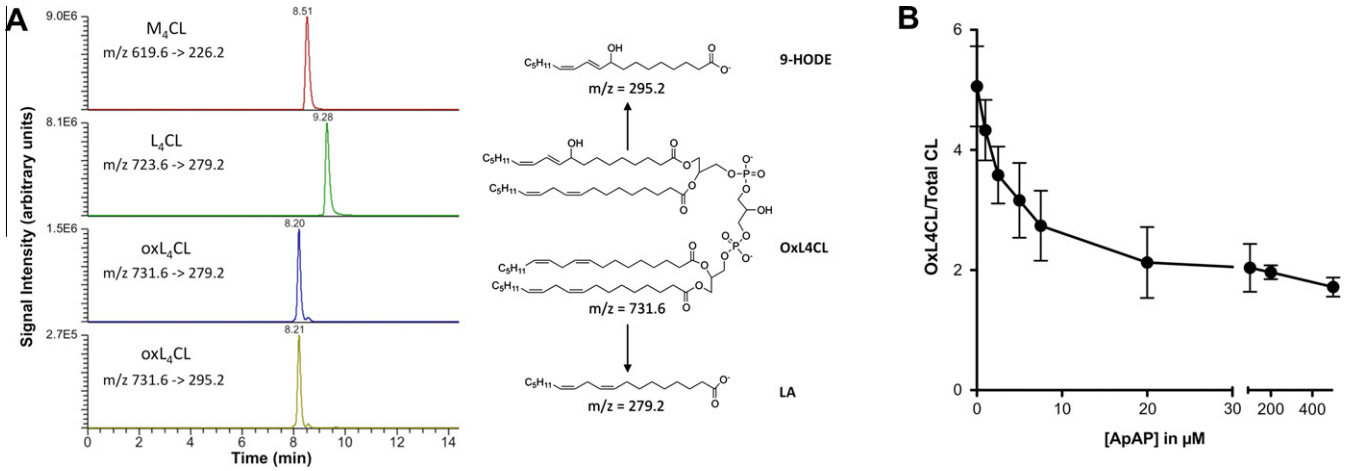

Fig. 2. ApAP inhibits cyt c-catalyzed oxidation of cardiolipin. (A) Analysis of oxidation products of L_4CL by LC-MS. The following transitions were monitored: M_4CL, m/z 619.6 to 227.2; L_4CL, m/z 723.6 to 279.2; oxL_4CL, m/z 731.6 to 279.2 and 731.6 to 295.2. The structures of the doubly charged molecular ion $[L_4CL\text{-}OH - 2H]^{2-}$ and of the monitored fragments are represented for OxL_4CL. M_4CL: tetramyristeoylcardiolipin. L_4CL: tetralinoleoylcardiolipin. OxL_4CL: monohydroxyL_4CL. (B) L_4CL liposomes were incubated with cyt c with various concentrations of ApAP and oxidized CL were quantified by LC/MS as described in the methods section. Oxidized CL are represented as % of total CL (mean ± S.E.M., n = 6).

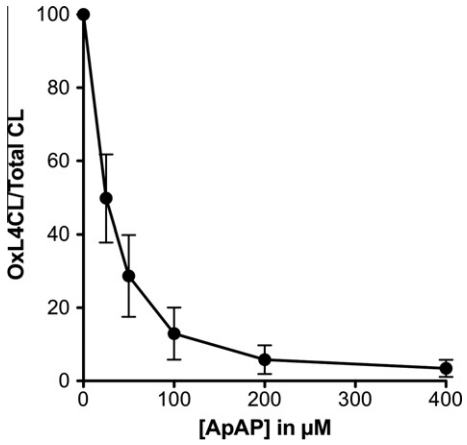

Fig. 3. ApAP inhibits CL oxidation in isolated mitochondria. Mouse liver isolated mitochondria were pretreated with various concentrations of ApAP for 1 h prior being activated by tBid. CL and its oxidized products were extracted and analyzed by LC/MS as described in the methods section. Oxidized CL is expressed as % of total CL (mean ± S.E.M., $n = 6$).

ApAP is very efficient in inhibiting the prostaglandin synthases which are located in the endoplasmic reticulum, it has not been determined if ApAP also penetrates in the mitochondria. Using our mass spectrometric assay we investigated whether ApAP could inhibit CL oxidation in isolated mitochondria. The mitochondria were activated with tBid, as it was shown that this led to increased CL oxidation [24]. Our results clearly demonstrate that ApAP inhibits CL oxidation in isolated mitochondria with an IC_{50} similar to that observed using L_4CL liposomes and purified cyt c. These data support the hypothesis that ApAP penetrates in the mitochondria and inhibits cyt c-dependent lipid peroxidation in response to tBid.

Our results may have broad potential implications as cyt c-catalyzed lipid peroxidation is involved in several biochemical processes. Oxidative stress is known to induce oxidation of phospholipids in the mitochondria by a cyt c-dependent mechanism [1–3,32] which has recently been shown to inhibit mitochondrial function and initiate the apoptotic response in a Bid-dependent fashion [33].

Cyt c also oxidizes phospholipids in the plasma membrane. An elegant work by Tyurina et al. suggested that cyt c binds to phosphatidylserine (PS) in the plasma membrane and catalyzes its peroxidation, leading to PS externalization [15], a trigger for phagocytic elimination of apoptotic cells [34,35].

A seminal discovery made by Kagan et al. suggests that CL peroxidation appears to be an early event preceding the release of cyt c and caspase activation [20]. The presence of four linoleic acid acyl chains in one molecule and the mitochondrial location make it susceptible to free radical oxidation [36]. The oxidation of CL is catalyzed by a peroxidase activity of the cyt c/CL complex. As a heme protein, cyt c can function as a peroxidase, albeit at a very low rate (about 1 $M^{-1}S^{-1}$) [37,38]. Native cyt c favors its normal function as an electron shuttle between complex III and IV of ETC. However, binding of CLs to cyt c unfolds the protein and paves the way for an opening of the heme catalytic site to hydrogen peroxides [25,26]. We provide evidence that ApAP inhibits CL oxidation induced by the peroxidase activity of cyt c/CL complex by inhibiting cyt c/CL peroxidase redox cycling.

As discussed above, cyt c redox cycling could have deleterious effects independent of caspase activation by catalyzing lipid peroxidation in the mitochondria, which leads to impaired respiratory function, or at the cell surface, which may eventually lead to cellular death. In this context, our results suggest that inhibition of cyt c catalyzed lipid peroxidation by ApAP could provide cytoprotection by preserving mitochondrial function as well as preventing activation of the phagocytic and caspase pathways.

In previous studies, we have demonstrated that ApAP is capable of inhibiting redox cycling of other hemoproteins, specifically myoglobin and hemoglobin [19]. ApAP also has been found to inhibit myeloperoxidase-induced lipid peroxidation [39]. Together with our results presented herein, these findings suggest that ApAP is a pleiotropic inhibitor of peroxidases, including cyt c. Although sustained inhibition of apoptosis by inhibiting cyt c catalyzed oxidation of cardiolipin could potentially allow damaged cells to survive and accumulate additional mutations, leading to activation of oncogenes and uncontrolled cell proliferation (neoplasia), a pharmacologic approach that could temporarily prevent apoptotic cell death could have a profound beneficial impact in a variety of diseases such as myocardial infarction, stroke, and traumatic brain injury.

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