Does aspirin-induced oxidative stress cause asthma exacerbation?

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Abstract

Aspirin-induced asthma (AIA) is a distinct clinical syndrome characterized by severe asthma exacerbations after ingestion of aspirin or other non-steroidal anti-inflammatory drugs. The exact pathomechanism of AIA remains unknown, though ongoing research has shed some light. Recently, more and more attention has been focused on the role of aspirin in the induction of oxidative stress, especially in cancer cell systems. However, it has not excluded the similar action of aspirin in other inflammatory disorders such as asthma. Moreover, increased levels of 8-isoprostanes, reliable biomarkers of oxidative stress in expired breath condensate in steroid-naïve patients with AIA compared to AIA patients treated with steroids and healthy volunteers, has been observed. This review is an attempt to cover aspirin-induced oxidative stress action in AIA and to suggest a possible related pathomechanism.

Key words: aspirin-induced asthma, free radicals, isoprostanes, nasal polyps.

Introduction

Acetylsalicylic acid (ASA) is a common drug in use today. So far, it is mainly known for its analgesic, antipyretic and anti-inflammatory action. However, when used daily, aspirin has also been seen to display antithrombotic properties which are helpful in lowering the risk of heart attack [1, 2], clot-related strokes [3, 4] and other blood flow problems. However, in the space of a few years there have been reports associating it with other completely new, very interesting properties.

Firstly, researchers have noticed that aspirin may intensify fat burning and reduce fatty liver in obese mice [5]. Many population studies have also shown an association between a reduced risk of Alzheimer's disease (AD) and use of non-steroidal anti-inflammatory drugs such as aspirin [6], which may well be related to alleviating inflammation associated with pathogenesis of AD [7].

For some time, aspirin has also been thought to possess anti-tumor properties. In a certain dose (75–100 mg) it helps to prevent certain cancers and reduces the risk of death from cancer by 40% for colorectal cancer, 60% for esophageal cancer, 30% for lung cancer and 10% for prostate cancer [8]. Direct inhibition of cyclooxygenase-2 (COX-2) activity is the main mechanism by which aspirin has been proposed to inhibit the development of certain cancers [9], although other mechanisms have

also been hypothesized, some of which also indicate that aspirin may cause oxidative stress and thus induce cancer cell apoptosis.

It is known that oxidative stress is the imbalance between the production of oxidants (reactive oxygen (ROS) and nitrogen (RNS) species including superoxide ($O_2^{\cdot-}$), hydrogen peroxide (H_2O_2), hypochlorite (ClO^-), hydroxyl radical (OH^-), nitric oxide (NO), and peroxynitrite ($ONOO^-$)) and endogenous antioxidant defenses in cells. Antioxidant compounds constitute urate, glutathione, ubiquinone and thioredoxin; moreover, some proteins – ferritin, transferrin, lactoferrin, caeruloplasmin – acting as antioxidants, bind some transition metals that may start oxidative reactions. However, the antioxidant enzymes crucial for protection of the airway include, primarily, superoxide dismutases (SOD) and glutathione peroxidases (GPx). Superoxide dismutases convert superoxide to hydrogen peroxide, whereas GP removes hydrogen peroxide and lipid hydroperoxides. This GPx mechanism involves glutathione (GSH), which acts as a co-substrate and is itself oxidized to glutathione disulfide (GSSG) (Figure 1).

Allowedly mitochondria are the major site of intracellular ROS production due to electron leakage along the respiratory chain [10], but it may also arise from plasma membrane systems, endoplasmic reticulum, lysosomes, peroxisomes and cytosolic enzymes. However, exogenous sources of ROS production have been linked to asbestos, ozone, coal, diesel fuels and cigarette smoke [11, 12].

At low concentrations, ROS/RNS exert a number of beneficial effects including immune-mediated defense against pathogenic microorganisms [13]. In turn, high levels of these species can damage DNA, lipids, proteins and carbohydrates, leading to an enhanced inflammatory response in respiratory airways as seen in asthma [13, 14].

Adverse oxidative stress can be a consequence of *inter alia* chronic hypernutrition, unhealthy diet, sedentary lifestyle and environmental overexposure. Such activities may be additional factors that escalate mitochondria dysfunction, reduction of antioxidant resources and significantly stimulate intercellular pathways leading to oxidative stress. In some cases, an excessive oxidative burden leads to clinical signs, but it is ascribed to cumulative effects of multiple activities [15].

Oxidative stress in asthma

Oxidative stress is rapidly gaining recognition as a key phenomenon in chronic diseases and in the case of asthma, various environmental pollutants, oxidants and drugs may induce oxidative burden in mitochondria of airway epithelial cells, resulting in the release of proinflammatory mediators, which recruit various types of inflammatory cells including eosinophils, neutrophils, lymphocytes and macrophages [16]. Additionally, stimulated inflammatory cells release various kinds of ROS which damage surrounding tissues in the airway.

Based on a variety of studies, it is clear that pulmonary ROS formation is a component of the molecular mechanism of asthma. The framework of ROS generation is such that oxidants mediate inflammatory responses and activate pro-inflammatory cytokine (TNF-α, IL-1β, IL-8, IL-6) and chemokine genes that facilitate the up-regulation of adhesion molecules and the increased release of pro-inflammatory mediators [17]. Many known inflammatory target proteins such as matrix metalloproteinase-9 (MMP-9), intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), cyclooxygenase-2 (COX-2) and cytosolic phospholipase ($cPLA_2$) are also associated with NADPH oxidase (NOX) activation and ROS overproduction [18–22]. Moreover, the morphological and functional properties of endothelial cells such as permeability and expression of adhesion molecules can be altered by ROS, leading to adhesive interaction between inflammatory and endothelial cells which may contribute to the expression of inflammatory symptoms [23]. More explicitly, ROS may act as signaling modifiers of such transcription factors as nuclear factor-κB (NF-κB) and activator protein-1 (AP-1) in epithelial cells, resulting in activation of many of the above-mentioned pro-inflammatory cytokines, enzymes and adhesion molecules [13, 24–27]. Oxidative stress has been proven to affect smooth muscle contraction [28], induce airway hyper-responsiveness [29], and increase mucus secretion and epithelial shedding within respiratory cells [30, 31]. In turn allergens, gaseous pollutants, bacteria and viruses activate inflammatory cells in asthmatic airways and cause respiratory burst releases of ROS to surrounding respiratory cells and tissues [32]. Many studies have revealed that patients with asthma demonstrated increased production of ROS, which correlates with severity of airflow limitation and the degree of airway

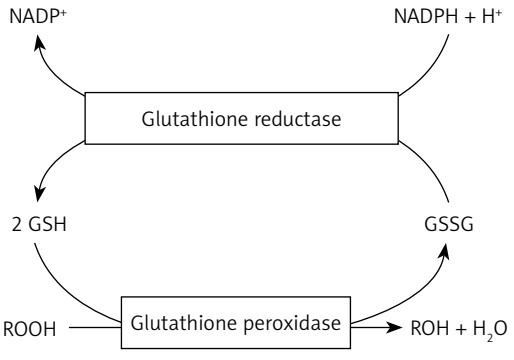

Figure 1. Diagram of glutathione homeostasis

hyperresponsiveness, as quantified by methacholine challenge [33–36]. Indeed, ROS induce direct contraction of airway smooth muscles, hyperresponsiveness, and this effect is enhanced when the epithelium is injured. Neutrophils isolated from peripheral blood of asthmatics generate greater amounts of ROS than cells from normal subjects, and their ability to produce ROS correlates with the degree of airway hyperresponsiveness to inhaled methacholine [37, 38]. Eosinophils derived from peripheral blood produce greater amounts of ROS after stimulation *ex vivo* in asthma, which also correlates with bronchial hyperresponsiveness [39–41]. Thus, this observation may suggest that ROS play a pivotal role in the pathogenesis of asthma and provide a link between epithelial injury arising from a variety of causes and airway hyperresponsiveness [42].

While much of the evidence for the involvement of ROS in the pathogenesis of asthma is indirect, numerous markers of oxidative burden have been measured [43]. Evaluation of levels of these markers is very beneficial in clinical investigations because it relates to severity of disease and provides a reproducible method for monitoring asthma. Exhaled air, exhaled breath condensate (EBC), induced sputum and bronchoalveolar lavage fluid (BAL) are biological samples that are often utilized for assessing oxidant burden in the airways.

One of them, exhaled nitric oxide (NO), has been identified as a potential marker to monitor airway inflammation and oxidative stress in asthma. Exhaled NO is increased in patients with asthma compared with normal subjects [44, 45], increased in allergen-induced late asthmatic reactions [46] and reduced when asthma exacerbations are treated with corticosteroids [47]. Is has also been proven that the level of FeNO positively correlates with measures of asthma control, as defined by recent symptoms or dyspnea, use of rescue medications, reversibility of airflow obstruction [48], level of sputum eosinophils and airway hyperresponsiveness [49], and the main site of origin of the increased levels of FeNO in asthma is the lower airways [45].

In the respiratory system, NO derived from constitutive NO synthase (cNOS) has homeostatic effects including dilatation of pulmonary blood vessels [50] and relaxation of airway smooth muscle. In turn, massively produced NO derived from the inducible type of NOS (iNOS, NOS2), which reacts with superoxide anion and produces reactive nitrogen species (RNS) such as peroxynitrite, has been reported to play a key role in airway and lung inflammation [51, 52]. Thus enhanced NOS2 expression in the airways of asthmatic patients is responsible for the increased NO levels in the exhaled breath [53, 54].

Other exhaled markers of oxidative burden in asthma are H_2O_2 and CO. It has been shown that the levels of exhaled CO are elevated in stable asthma and become reduced towards the normal value by administration of inhaled corticosteroids [55]. However, in the case of hydrogen peroxide, exhaled H_2O_2 concentrations are higher in smoking than nonsmoking subjects [56], intermittent, mild-moderate asthmatics than healthy subjects and steroid-untreated and steroid-treated asthmatics than healthy subjects [57]. Excessive smoking leads also to a further elevation in exhaled H_2O_2 levels in asthmatic patients, indicating that smoking contributes to an acute release of ROS in the airways [58].

The next important tool for reliably exploring oxidative stress in asthma is 8-iso-prostaglandin $F_{2\alpha}$ (8-isoprostane). Elevated EBC 8-isoprostane concentrations have been reported in asthmatic children [59, 60] and adults with severe asthma in comparison to healthy controls [61], and these concentrations increase with asthma severity [61, 62]. EBC 8-isoprostane levels decrease after allergen avoidance in children with allergic asthma [62, 63], and smoking elicits an acute 50% increase in EBC 8-isoprostane levels within 15 min [64]. The level of 8-isoprostane seems to be higher in sputum than in EBC [65], and sputum concentrations of 8-isoprostane are also higher in adults with stable asthma than in healthy subjects [66]. However, the concentrations of *inter alia* 8-isoprostane do not coincide between EBC and BAL [67], but it is worth noting that BAL is too invasive and not sensitive enough to be utilized in the assessment of oxidative stress and airway inflammation in clinical practice.

It is also known that elevated levels of GSSG can be considered a marker of oxidative stress, whereas increased total or reduced GSH levels are thought to represent an adaptive response to the increased oxidative stress in the lungs. Patients experiencing an acute exacerbation of asthma revealed GSH levels lower than stable asthmatics, but still significantly higher than those of healthy controls [68]. Thus, from the clinical point of view, a decreased level of antioxidant enzymes, including systemic SOD, is related to airflow limitation and asthma aggravation [69].

Genetically determined host responses to oxidative stress also appear to be critical [70]. Genetic polymorphisms in genes encoding antioxidant enzymes may be significant risk factors for asthma. For example, the presence of polymorphisms of the glutathione-S-transferase gene was correlated with the response to second-hand smoking in asthmatic children [71].

Taken together, the evidence suggests that oxidative stress plays a major pathophysiological role

in asthma and it is important for the severity of this condition. At the same time, either ROS generation or endogenous antioxidant mechanisms are out of balance, which causes that a more inflammatory state becomes apparent. Moreover, oxidative stress represents a greater predisposition to exacerbation of asthmatic symptoms after environmental exposure to various organic chemicals (diesel exhaust, cigarette smoke) that increase the secretion of ROS.

Aspirin-induced asthma

Three years after introducing aspirin to the market, the first case of asthma exacerbation by aspirin was reported. Nowadays, up to 20% of adult asthmatics with nasal polyps are sensitive to aspirin and other non-steroidal anti inflammatory drugs (NSAIDs) [72]. The first symptoms of aspirin-intolerant asthma (AIA), occurring within 2 h after ingestion of ASA, include bronchospasm accompanied by nasal congestion and/or rhinorrhoea. Generally AIA, also named as aspirin-exacerbated respiratory disease (AERD), ASA triad, and Samter's syndrome, is characterized by chronic rhinosinusitis, nasal polyps, severe bronchial asthma and intolerance to ASA or other NSAIDs.

So far, no unambiguous theory exists which provides a satisfactory explanation for the pathogenesis of AIA. One hypothesis explaining the pathogenesis of AIA is the cyclooxygenase theory. According to it, aspirin inhibits intracellular COX enzymes, inhibiting prostaglandin biosynthesis. In turn, inhibition of COX causes an imbalance between the synthesis of eicosanoids originating from the cyclooxygenase pathway, which have smooth muscle relaxant properties, in favor of the synthesis of lipoxygenase pathway eicosanoids contracting bronchitis (15-hydroxyeicosatetraenoic (15-HETE) acid [73], LTB_4 [74], cysteinyl leukotrienes – cysLTs [75, 76]).

Alternatively, an equally important possibility explaining the pathogenesis of AIA is the diminished capacity for synthesis of lipoxins (LXs) [77]. The LXs are 15-lipoxygenase products that, in contrast to leukotrienes, have anti-inflammatory properties; they inhibit chemotaxis, transmigration across endothelial and epithelial monolayers, diapedesis and superoxide anion generation by polymorphonuclear leukocytes [78]. Thus, impairment of the balance between lipoxin and leukotriene production may be a key in the pathogenesis of aspirin hypersensitivity.

Apart from biochemical theories of aspirin-induced asthma, in the literature there is also a large amount of data concerning genetic mechanisms, suggesting the involvement of various genes. Some of them are associated with the arachidonic acid pathway (LTC4S [79], COX2 [80], cysLTR1 [81], cysLTR2 [82]), and some are related to eosinophilic inflammation (ACE [83], CCR3 [84], NLRP3 [85], TBX21 [86]) and pathogenesis of nasal polyps (TGF-β1 [87]). There are also gene polymorphisms whose relationship with AIA is not fully ascertained (FSIP1 [88], CEP68 [72], SLC22A2 [89, 90], ADAM33 [91], EMID2 [92], TLR3 [93], ADORA1 [94], CACNG6 [95], WDR46 [96], ZNRD1 [97], KIFC1 [98], CYP2C19 [99]).

Recently, there has been a great deal of discussion about 8-isoprostanes, reliable biomarkers of lipid peroxidations which are stable prostaglandin-like arachidonate products formed on membrane phospholipids by the action of reactive oxygen species [100]. Structure-activity studies with 8-isoprostanes have revealed that E-ring compounds are more potent than F-ring compounds, doubly unsaturated compounds are more potent than singly unsaturated compounds, and the α configuration is more potent than the β configuration [101] (Figure 2).

Moreover, the 8-isoprostanes have a higher contractile potency in human large airways compared with human small airways [102]. The two exceptions are 8-iso-PGE_1, which have highly variable potency in both preparations, and 8-iso-$PGF_{3\alpha}$, which have powerful relaxant effects in human large airways [50]. Increased levels of 8-isoprostane have been found in expired breath condensate in steroid-naïve patients with AIA compared with steroid-treated patients with AIA and healthy control subjects [103]. Thus, the presence of 8-isoprostane in breath condensate appears to reflect oxidative stress and is progressively increased with the severity of asthma [61]. It is probable that the intensity of inflammation, as reflected by oxidative stress in the airways of patients with AIA, is greater than in subjects with ATA.

Mechanisms underlying aspirin-induced oxidative stress and apoptosis

The majority of the research concerning mechanisms of aspirin action have mainly been carried out in cancer cell systems. However, it has not excluded the similar action of ASA in other inflammatory disorders.

So far, numerous studies have demonstrated that aspirin treatment with 5 and 10 µmol/ml for 24 and 48 h induces oxidative stress, leading to apoptosis and alterations in signal transduction, mitochondrial respiratory function and cell cycle arrest [104–107].

In addition, other effects of ASA treatment include reduced expression of the anti-apoptotic protein Bcl-2, marked depletion of the GSH pool and increased reactive oxygen species production [107].

Bcl-2 plays a regulatory role in the transport of GSH into the mitochondria under oxidative

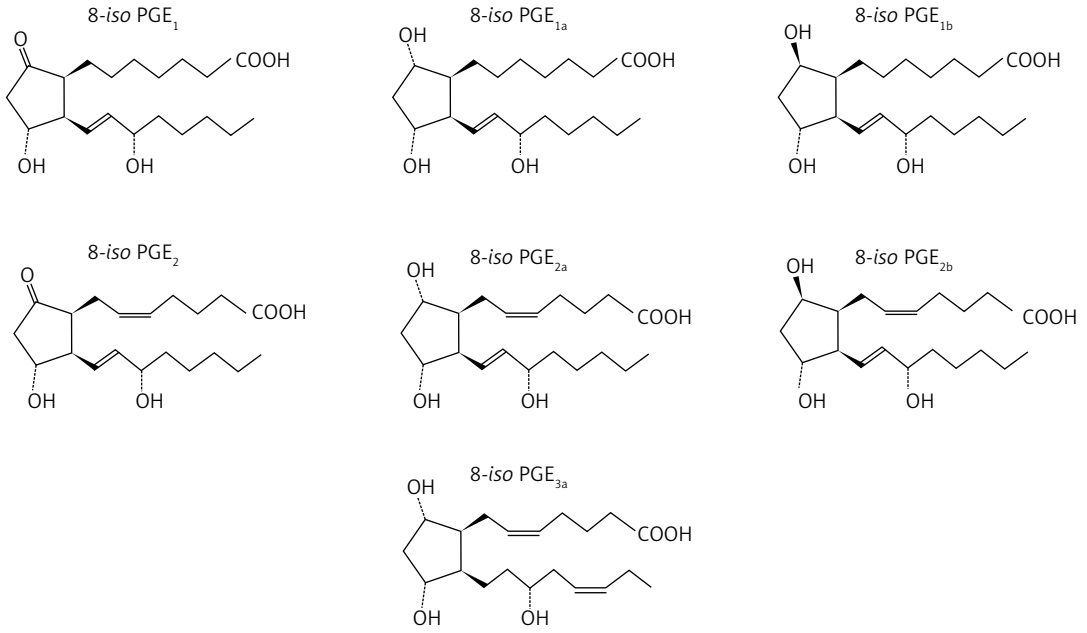

Figure 2. Chemical structures of ascertained isoprostanes

stress conditions [107], and downregulation of this protein might also be the cause of mitochondrial membrane potential depletion. Thereafter, decreased expression of Bcl-2 may also cause TRAIL-induced apoptosis by activation of caspases, induction of conformational change, translocation of Bax and cytochrome c release during aspirin treatment [108–111]. Generally, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is a cytotoxic molecule that has been shown to exert antitumor cytotoxic effects with minimal toxicity to normal tissues [112, 113]. In combination with NSAIDs, including aspirin, TRAIL may increase antitumor activity, leading to cell apoptosis [114, 115]. Both TRAIL and tumor necrosis factor (TNF)-α are known to bind to their cell surface receptors leading to caspase-8 activation. Activated caspase-8 multiplies the apoptotic signal either by activating other caspases or by cleaving BH3 domain-only proteins such as Bid in the Fas signaling pathway [116]. Bid translocates to the mitochondria from the cytosol to induce mitochondrial damage and activate Bax to form Bax multimers [117]. In a further response to apoptotic stimuli, Bax undergoes a conformational change and integrates into the mitochondrial membrane, inducing release of cytochrome c, and activation of caspase-9 and thus caspase-3 [118]. Caspase-3 is the most likely candidate for a mammalian cell death regulator induced by aspirin by cleaving many proteins, such as DNA repair enzyme poly(ADP-ribose) polymerase (PARP) and DNA fragmentation factor 45, leading to the typical 180 bp DNA strand breaks [119]. Cytochrome c release into the cytosol forms a complex with Apaf-1 and the proform of caspase-9 and, in the presence of ATP, this complex triggers a cascade by activating other caspases (3, 6 and 7) [120].

In turn, the factor that probably may be responsible for the reduced expression of Bcl-2 protein is NF-κB [121]. Previous studies have shown that aspirin inhibits the transcription factor NF-κB [106], which is mediated through preventing the phosphorylation and degradation of the inhibitory subunit IκB [122]. Furthermore, a more precise study has shown that aspirin-induced proteasomal dysfunction is responsible for prevention of the degradation of IκB and thereby blocking NF-κB activation [123]. The ubiquitin proteasome system (UPS) is the major lysosomal pathway of cells responsible for the short-lived, misfolded protein and the degradation of several transcription factors in eukaryotes [124]. It also includes proteins involved in cell survival, and it is believed that the dysfunction of this pathway will activate apoptotic signaling pathways and cell death [125, 126].

Another relative molecular mechanism by which aspirin may exert its apoptotic action is abrogation of the IL-6-IL-6R-STAT3 signaling pathway [127]. In general, IL-6 sends its signal into the cell by forming a complex with IL-6R and leads to activation of the receptor associated kinases of the JAK family. In turn, kinases phosphorylate the tyrosine residue (705) present in the transcription factor of the signal transducer and activator of transcription 3 (STAT3) [128]. Following this, STAT3 dimerizes and translocates into the nucleus, inducing the expression of such target genes as cyclin D1, XIAP and Bcl-2. It has been reported that the activation of NF-κB is crucial for the inducible expression of IL-6 expression [129], emphasizing once more participation of NF-κB in aspirin-induced apoptosis (Figure 3).

In addition, either a decreased level of GSH or elevated ROS number was found to be accompanied by an increase in lipid peroxidation (LPO), which presumably plays a substantial role in oxidative stress-induced mitochondrial dysfunction and apoptosis [107, 130]. On the other hand, treatment with NAC, a GSH synthesis precursor, resulted in partial protection from LPO, suggesting the protective role of mitochondrial GSH metabolism in membrane lipid peroxidation [131].

Oxidative stress-dependent mitochondrial permeability transition also leads to loss of membrane potential and inhibition of mitochondrial bioenergetics [107, 132]. It has been demonstrated that ASA causes a significant decrease in ATP levels accompanied by inhibition of the activities of the respiratory chain enzymes NADH:ubiquinone oxidoreductase (complex 1) and cytochrome c oxidase (complex IV), as well as the mitochondrial matrix enzyme aconitase as a marker for mitochondrial oxidative stress [107]. Application of NAC has also been found to attenuate the marked reduction of ATP level that was supported by the recovery in complex 1 activity in ASA-treated cells [131]. However, lack of recovery of cytochrome c oxidase and aconitase activity suggests that mitochondrial GSH is selectively involved in regulating the activities of the respiratory complexes. It may be attributed to their extremely sensitive responses towards oxidative stress, ROS, NO and glutathionylation of proteins [132].

A recent study has also shown that HepG2 cells were arrested in the G0/G1 phase followed by apoptosis after ASA treatment [107]. It is likely that downregulation of Bcl-2 [133], or interference in signaling via prostaglandin E_2-dependent epidermal growth factor receptors and prostaglandin E_2- dependent cell surface receptors may contribute to G0/G1 cell cycle arrest [134, 135] (Figure 4).

The NSAIDs-induced endoplasmic reticulum stress also seems to be connected with the mechanism of apoptosis. The accumulation of unfolded protein in the endoplasmic reticulum (ER) induces what is known as the unfolded protein response (UPR) [77] transduced by three transmembrane proteins: inositol-requiring enzyme 1 (IRE1), PKR-like ER kinase (PERK) and activating transcription factor 6 (ATF6). Cells initially adapt to the accumulation of unfolded proteins by inducing ER-resident stress proteins (chaperons) such as glucose-regulated protein GPR78 that refold the unfolded proteins. These mentioned UPR components are bound to the ER chaperone GPR78 in nonstressed conditions. However, during ER stress GPR78 is separated, leading to their activation. However, if this adaption is not sufficient, the apoptotic response is initiated by CHOP (CCAAT/enhancer-binding protein homologous protein). Treatment with NSAIDs has demonstrated induction of GRP78 and CHOP protein [136]. Studies have also shown that oxidative stress is a strong inducer of UPR in nasal polyps (one of the main symptoms of AIA) cells [137]. It is suggested that ROS trigger UPR by modifying the redox state of the ER lumen, which generates impaired disulfide bonds in maturing proteins [138]. What is more, UPR seems to be linked with the lipoxygenase signaling pathway, because increased LTB_4 secretion under UPR induction in nasal polyp cells has already been proven [137]. Therefore UPR may be related to chronic inflammation observed in nasal polyps enforcing recruitment of neutrophils.

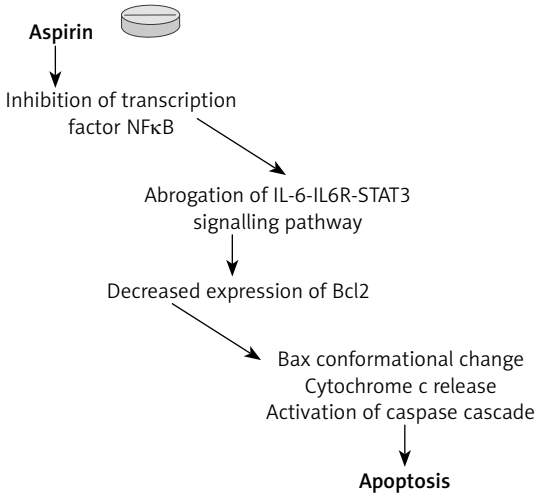

Figure 3. Apoptotic mechanism of aspirin action. According to the results, aspirin leads to inhibition of NFκB and next reduces Bcl2 protein expression. In turn, Bcl2 protein reduction causes TRAIL and TNF-α-induced apoptosis by activation of various caspases, conformational change and translocation of Bax and cytochrome c release. Another relative molecular mechanism of aspirin is abrogation of IL-6-IL6R-STAT3 signalling pathway that may also result in reduction of Bcl2 protein expression

As well as high levels of malondialdehyde (MDA), one of the metabolites of free radical-mediated lipid peroxidation was also demonstrated in nasal polyp tissues [139, 140].

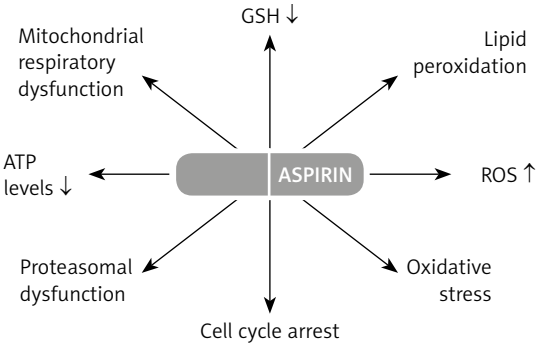

Figure 4. Various aspirin actions in cell

Conclusions

The lungs are directly exposed to a higher oxygen concentration than most other tissues, so they develop appropriate mechanisms to be protected against oxidants. However, excessive exposure to oxidizing agents may cause oxidative stress, resulting in the release of proinflammatory mediators, which then recruit inflammatory cells. Additionally, stimulated inflammatory cells release ROS that damage surrounding tissues in the airway, which positively correlates with the direct contraction of airway smooth muscles and greater hyperresponsiveness. Additionally, impairment in antioxidant defenses might be a critical point for asthmatic patients to aggravate lung functions in response to various factors as additional sources of free radicals such as exhaust fumes, cigarette smoke, radiation, certain chemical compounds and drugs. Regarding acetylsalicylic acid, a literature review has revealed half a dozen articles devoted to the aspirin-induced oxidative burden in cancer systems, but there is a lack of research explaining this discrepancy in asthma (possibly due to the enormous research effort invested in oncology at present and the urgent need to find safe and efficient cures). However, confirmation that aspirin may exacerbate oxidative stress in asthma will be very helpful and beneficial in understanding why some asthmatic patients have developed hypersensitivity to aspirin and why they are preponderantly adults. According to this theory, patients with acquired lung mitochondrial dysfunction as a pathophysiological mechanism in this disorder would have a tendency to develop AIA. Moreover, aspirin would constitute a factor that provokes oxidative stress in cells, which would be additionally supported by the inflammatory milieu.

To sum up aforesaid results, it cannot be excluded that oxidative stress might play a pivotal role in pathogenesis of AIA, but it will require a lot of research. So, we hope that this review may contribute to a greater interest in discovering new signaling pathways in aspirin-induced asthma by conducting multiple studies to confirm the aforementioned correlation.

Conflict of interest

The authors declare no conflict of interest.

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