Duchenne muscular dystrophy: Focus on arachidonic acid metabolites

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A B S T R A C T

Duchenne muscular dystrophy (DMD) is an incurable disease, characterized by the muscle inflammation and progressive deterioration of muscle function.

We discuss and review the role of arachidonic acid (AA) metabolites in DMD in muscle fiber degeneration and regeneration and new opportunities for developing new drugs by targeting the AA pathway, providing evidence that the AA pathway could represent an efficacious strategy to ameliorate the treatment of DMD patients. Currently a series of DMD care recommendations regarding management of rehabilitation, orthopedic, respiratory, cardiovascular, gastroenterology exist and the therapy is restricted to corticosteroids for muscle dysfunction with serious side effects. Nowadays there are still no effective cures for the disease. The alternative pharmacological strategies targeting the AA metabolites may yield favorable outcomes in DMD. 5-LOX inhibition might be important for the survival of myofibers. Moreover H-PGDS inhibitors, cyclooxygenase (COX)-inhibiting NO donors (CINODs), inhibitors of Ca2+ -independent PLA2 are some of the different pathways which can bring to further development of new drugs.

1. Introduction

Duchenne muscular dystrophy (DMD) is an X-linked disease, the most frequent form of muscular dystrophy, occurring in about 1 in 3500 live male births. The condition is caused by the mutation in the gene encoding for dystrophin, consisting of 79 exons in males. Dystrophin belongs to the dystrophin glycoprotein complex (DGC), a transmembrane protein complex that includes dystroglycans, sarcoglycans, dystrobrevins [1]. It is expressed in cardiac and skeletal muscles, and in the healthy muscle, and is located in the intracellular surface of the sarcolemma, beside with the sarcomeres, providing a link between the intracellular actin cytoskeleton and the extracellular matrix of skeletal muscle [2-5]. Lack of dystrophin disrupts the DGC complex and results in membrane instability, muscle degeneration and myofiber necrosis. DMD patients usually die because of cardiorespiratory failure [6]. Inflammation, oxidative stress, the persistence of inflammatory macrophages in the muscle, the reduction of the nitric oxide (NO), and alteration in cellular Ca2+ homeostasis contribute significantly to the pathogenesis. TNFα is a pro-inflammatory cytokine that contributes to the aggravation of the muscle degeneration, whereas TGF-β may mediate fibrosis and wound healing [7-9].

Although DMD is generally diagnosed at approximately 5 years of age, the diagnosis is suspected earlier due to delays in walking, frequent falls, calf hypertrophy, difficulty in climbing stairs, abnormal gait etc. [10]. Loss of independent ambulation is followed by respiratory, cardiac, and orthopaedic complications [11]. However, rehabilitative and orthopaedic interventions, combined with use of corticosteroids have reduced the risk of scoliosis and increased life expectancy in DMD patients. Correct diagnosis is very important and should be done by a neuromuscular specialist, supported by a geneticist who should clinically assess the child [10]. However, DMD is suspected either when transaminases are increased (such as aspartate aminotransferase, alanine aminotransferase), creatine kinase, and lactate dehydrogenase levels are increased (such as aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase), and electromyogram shows characteristic changes.

Abbreviations: DMD, Duchenne muscular dystrophy; DGC, dystrophin glycoprotein complex; AA, arachidonic acid; PG, prostaglandins; LT, leukotrienes; TX, thromboxane; L, lipoxins; HETE, hydroxyeicosatetraenoic acids; COX, cyclooxygenase; PLA2, phospholipase A2; iPLA2, Ca2+ -independent PLA2; LPS, lysophosphatidylcholine; NO, nitric oxide; nNOS, neuronal nitric oxide synthase μ; NDGA, nordihydroguaiaretic acid; PG, prostaglandins; mPGES, microsomal prostaglandin E synthase; MyoD, myoblast determination protein 1; prostacyclin, PGI2; PGDS, PGD synthase; L-PGDS, hematopoietic PGD synthase (H-PGDS) and lipocalin PGDS; PPAR-γ, peroxisome proliferator- activated receptor γ; GST, GSH S-transferase; tetranor PGDM, 11,15-dioic acid; FLAP, 5-LO activated protein; 5-HPETE, 5-hydroperoxyeicosatetraenoic acid; ATL, aspirin-triggered lipoxin; HQL-79, 4-benzhydryloxy-1-[3-(1H-tetrazol-5-yl)-propyl]-piperidine; CINODs, Cyclooxygenase (COX)-inhibiting NO donors; NDGA, nordihydroguaiaretic acid.

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aline aminotransferase), when serum creatine kinase is increased, or if abnormal muscle functions are observed [10].

Currently there is no cure for the disease. However different experimental therapy approaches, such as exon skipping, gene therapy, myostatin inhibitors, utrophin modulation, CRISPR/Cas9, suppression of stop codons, and stem cells, are being considered as promising methods to promote production of a functional dystrophin protein and to treat DMD.

To date, the majority of DMD therapies undergoing research, both in pre-clinical and clinical trials, have also focused on combined therapies by targeting different sites. The results of many therapies in preclinical studies are promising [12]. Studies in mice have shown that two metabolic targets are to increase AMPK and PPAR ß/δ by targeting diaphragm. Increasing enzymatic effects results have shown that treatment of DMD myotubes with adiponectin increased the inflammation and upregulated the utrophin in humans [13], whereas PDE inhibitors (sildenafil) reduced the exercise-associated ischemia in acute treatment, but failed to demonstrate improvements in chronic treatments [14,12]. Ricotti et al showed that SMT C1100, a utrophin modulator was safe in healthy volunteers and was well tolerated in DMD patients [15]. Allopurinol increased creatine phosphatase and ATP after 22 months, instead of unclear benefits shown after 27 months of treatment [16,17]. Hafner et al. showed that 16 weeks of treatment with L-Arginine and Metformin reduced oxidative stress and improved function in DMD patients [18]. A significant limiting factor is that all muscles must be targeted. In conclusion, despite the greater part of this data having come from animal-based studies, and despite the approval of etopirin by FDA, clinical trials are also moving forward, assessing in particular the effect of different combined therapies in DMD.

1.1. The effect of AA metabolites on muscle degeneration/regeneration processes in Duchenne Muscular Dystrophy

Arachidonic acid (AA) is a polyunsaturated fatty acid released by membrane phospholipids in inflammatory conditions, and gives rise to different metabolites such as: prostaglandins (PG), leukotrienes (LT), thromboxane (TX), lipoxins (LX), hydroxyeicosatetraenoic acids (HETE). The cyclooxygenase (COX) enzyme is responsible for the release of prostaglandin E2 compared to control subjects, in response to the high concentration of unsaturated fatty acids, such as oleic acid (18:1), linoleic acid (18:2), arachidonic acid (20:4) in DMD patients’ erythrocytes [25]. The same study indicated a significant increase of the concentration of palmitic acid (16:0), a saturated fatty acid in patients with DMD. Abnormalities in lipid metabolism were associated with changes in membrane composition and fluidity [25]. Reduced concentration of the polyunsaturated fatty acids in erythrocytes of DMD patients can lead to the alteration of calcium homeostasis and an increased cell membrane peroxidation, thereby increasing enzymatic efflux. Expression of COX-2 was upregulated and colocalized in skeletal muscle fibres of DMD patients at early stages of muscle fibre necrosis [26].

1.1.1. Prostaglandins

Prostaglandins are a group of lipid mediators that are produced from arachidonic acid through the cyclooxygenase pathway, and play an important role in muscle growth and differentiation. They are known to stabilize the sarcolemma and have beneficial effects on muscle fiber survival [21,27]. The skeletal muscle growth and repair depend on myogenesis [28]. For instance, myoblasts and inflammatory cells, release arachidonic acid metabolites, such as prostaglandins, that are responsible of controlling different steps of myogenesis, such as proliferation, differentiation, migration, fusion to myotubes/myofibres and survival of myoblasts [19,28,29].

Microsomal prostaglandin E synthase (mPGES) produces PGE2 from PH2. PGE2 is a potent mediator of inflammation and pain, and is produced by human myoblasts during proliferation and differentiation [19,29]. PGE2 might be also produced by recruited inflammatory cells, including macrophages, mast cells, and neutrophils in inflamed or injured muscle [19]. Moreover, mechanical stretch and mechanical stress increase PGE2 and PGF2α levels in the media of stretched myoblasts [29].

PGE2 enhances myogenic differentiation, as supported by the upregulated expression of myogenic regulatory factors, myoblast determination protein 1 (MyoD) and myogenin [30]. In addition, it has been suggested that PGE2 is a potential mediator of skeletal muscular wasting, despite controversial findings on the role of PGE2 on protein breakdown in isolated skeletal muscles [31,32].

Studies conducted in DMD patients and in Dmd mdx mutant mouse revealed that there is a higher production of PGE2 than in healthy tissues, probably associated with an increased activity of phospholipase A2 [33,34]. Jackson et al. showed that in the strips of biceps muscle from patients with Duchenne muscular dystrophy there was a higher release of prostaglandin E2 compared to control subjects, in response to a rise in intracellular calcium, which is probably associated with an increased activity of phospholipase A2 and with a higher number of regenerating fibres in the muscles of DMD patients [19,22,34].

PGI2 (prostacyclin) is another arachidonic acid metabolite which is produced by PGI synthase and acts through a G-protein coupled receptor (IP receptor). Bondesen et al. showed that prostacyclin receptor and PGI synthase are expressed in the primary mouse myoblasts, and that PGI2 regulates initial myotube formation via myoblast-myoblast fusion, yet does not appear to affect later myoblast-myotube fusion. Moreover, PGI2 is a negative modulator of myoblast migration [28]. Labarque et al. reported that the increase in bleeding tendency during spinal surgery of patients with DMD can result from increased platelet Gs activity after the release of natural prostacyclin (a Gs agonist) from the vessel wall. Prostacyclin inhibits platelet function and increases cAMP via Gs stimulation [35,36].

PGF2α is another arachidonic acid metabolite, whose receptor is expressed in differentiated muscle cells. PGF2α is produced by myoblasts, promotes cell fusion (myoblasts fusion with pre-existing myotubes), and can prevent myoblast apoptosis [37].

PGD2 is an AA metabolite produced in inflammatory cells, such as
mast cells, implicated in the development and resolution of inflammation. PGD synthase (PGDS) is the enzyme responsible for isomerization of PGH₂ to PGD₂ (Fig. 1). Two different types of PGDS are known: hematopoietic PGD synthase (H-PGDS) and lipocalin PGDS (L-PGDS), respectively. Unlike other prostanoids, PGD₂ and its product, 15 dPGJ₂ inhibit myogenesis, which is associated with peroxisome proliferator-activated receptor γ (PPARγ)-dependent and PPARγ-independent pathways. Veliça et al. demonstrated a new PGD₂ signalling mechanism during muscle repair mediated by high inflammatory associated PGD₂ concentrations, independent of the PGD₂ receptors (DP1 and DP2) [38]. H-PGDS is associated with the activity of GSH S-transferase (GST) involved in neuroinflammation and is induced in the necrotic muscle fibers of patients with Duchenne muscular dystrophy. Hyalinated fibers expressing HPGDS are increased in skeletal muscles of aged DMD patients [26]. Nakagawa group found that urinary 11,15-dioxa-9α-hydroxy-2,3,4,5-tetranorprostan-1,20-dioic acid (tetranor PGDM), a major PGD₂ metabolite, was increased in DMD patients [39]. This suggests that PGD₂-mediated inflammation plays a role in the pathology of DMD.

1.1.2. Thromboxanes
TXA₂ formation is implicated in platelet function deficiency in patients with DMD. Moreover, thromboxane B₂ (TXB₂) is an inactive product of TXA₂, which was found in the interstitial space of skeletal muscle. No further studies have been done to assess the role of TXB₂ in DMD.

1.1.3. Leukotrienes
5-LOX pathway gives rise to leukotrienes, which stimulate Ca²⁺ release, increase reactive oxygen species production [21,40] and stimulate TNFα production. LTB₄ is produced in the skeletal muscle of both patients and healthy controls determined by microdialysis [41], and is a powerful chemoattractant for myeloid cells and promotes the differentiation of T cells. LTB₄ is an important regulator of myogenesis, promotes the proliferation and differentiation of satellite cells. LTB₄ receptor (BLT1) is a G-protein coupled receptor expressed in macrophages, smooth muscle cells, neutrophils, and endothelial cells [42]. Enhanced expression of 5-LO mRNA, has been reported in muscle tissues from patients with polymyositis and dermatomyositis, indicating a role of 5-LO in these diseases [43]. On the other hand, LTC₄, LTD₄, LTE₄ enhance vascular permeability and smooth muscle contraction.

1.1.4. Isoprostanes
Isoprostanes are markers of inflammation produced by free radical–induced peroxidation of arachidonic acid in inflammatory conditions, such as atherosclerosis, diabetes, and Alzheimer disease. Grosso et al. has shown increased levels of isoprostanes in patients with DMD compared to healthy subjects, suggesting that oxidative stress may act as a supplementary cause of muscular cell damage in these patients for their entire life [44].

1.1.5. Hydroxyeicosatetraenoic acids
Arachidonic acid is converted by 5-LO and 5-LO activated protein (FLAP) into 5-hydroxyeicosatetraenoic acid (5-HETE), 5-hydroxyeicosatetraenoic acid (5-HETE), 5- hydroxyeicosatetraenoic acid (5-HETE), leukotriene A₄ (LTA₄), leukotriene B₄ (LTB₄), leukotriene C₄ (LTC₄), leukotriene D₄ (LTD₄), leukotriene E₄ (LTE₄), 12-keto leukotriene B₄ (12-keto LTB₄).

Fig. 1. Arachidonic acid cascade. Arachidonic acid is a substrate for different pathways and enzymes giving rise to several metabolites. Prostaglandins and thromboxane are produced via the COX-pathway, unlike leukotrienes that are produced via 5-LO pathway.
proliferative, and pro-resolving actions of lipoxins in mdx mice have already been reported [47]. The lipoxin receptor FPR2 is used as a tool for identifying compounds for the treatment of Duchenne muscular dystrophy.

Regarding inflammatory mechanisms in DMD, the arachidonic acid pathway and its mediators such as: PGE₂, PGD₂, PGF₂α, PGD₂, TXA₂, TXB₂, LTB₄, and isoprostanes are implicated in DMD pathogenesis, as above mentioned. Thus, we emphasize the need to understand the underlying mechanisms of those mediators and their role in inflammation, as important therapeutic targets for DMD patients. The capability of these mediators to enhance or slow the inflammation (lipoxins) present in DMD, makes such mediators useful in the development of the next generation of DMD drugs by targeting the AA pathway, as a strategy to attenuate DMD pathogenesis.

1.2. Effects of anti-inflammatory agents in DMS

Inflammation appears to play a role in the DMD pathogenesis. Corticosteroids (e.g. prednisone/prednisolone/deflazacort) suppress muscle inflammation by inhibiting the activity of PLA₂ and still form the basis for the pharmacological treatment of Duchenne muscular dystrophy [48]. Clinical trials have demonstrated that corticosteroids improve muscle function and strength, stimulate myoblast proliferation, reduce the cytosolic calcium concentration, inhibit muscle proteolysis and up regulate utrophin [49-52]. Uncertainty remains about the pathway through which glucocorticoids exert their effect in DMD, other than immunosuppression and reduction of inflammation. Despite contradictory studies demonstrating that the therapeutic effect of prednisolone is independent of the action of T and B-cells [53,54], it was proposed that corticosteroids stabilize the sarcolemma in muscle fibers [55]. Glucocorticoids exert both an inhibitory effect on protein synthesis and a stimulatory effect on muscle proteolysis [41]. Despite posing that corticosteroids can decrease the urinary tetranor PGDM concentrations in DMD patients, Nakagawa et al. showed that the benefits of corticosteroids are not mediated through PGD₂-related inflammation.

Moreover, considering that iPLA₂, lipid product LPS triggers opening of store-operated channels, inhibition of iPLA₂ and LPS can be important to protecting dystrophic fibers from excessive Ca²⁺ entry [24]. Daily use of glucocorticoids is preferred to alternative regimens. Prednisone, prednisolone, and deflazacort are believed to have a similar effect in altering the decline in motor, respiratory or cardiac function in DMD [10,54]. Deflazacort is the most preferred because it has a slightly different chronic risk profile, and slightly lower risk of weight gain with respect to prednisone. Glucocorticoid treatment is not recommended for children under 2 years old, who are still developing motor skills until 4-6 years old [10,56]. In patients who have used glucocorticoids while ambulatory, it is preferred to continue the medication after the loss of ambulation, in order to preserve upper limb strength, reduce the progression of scoliosis, and delay the decline in cardiac and respiratory functions [10,54].

Non steroidal anti-inflammatory drugs (NSAIDs) act mainly by inhibiting the cyclooxygenase enzyme, inhibiting the production of eicosanoids. Different studies have been performed to assess the role of NSAIDs in DMD. Serra et al. showed that NSAIDs are closely comparable to glucocorticoids in reference to their anti-inflammatory action [57]. They do not affect the isometric tension, utrophin levels, or the percentage of regenerating myofibers, despite contributing to the reduction of macrophage infiltration, resistance to fatigue and improvement of muscle morphology. Moreover, Serra et al. demonstrated that among three NSAIDs studied (acetylsalicylic acid, ibuprofen, and parecoxib), acetylsalicylic acid appeared to be less effective compared to the specific COX-2 inhibitor, parecoxib, which controlled utrophin expression.

H-PGDS inhibitors may be promising drugs for suppression of inflammation and muscular dystrophy. 4-benzhydroxyloxy-1-[3-(1H-tetrazol-5-yl)-propyl]-piperidine (HQL-79) was developed as an anti-inflammatory drug, as an antagonist for histamine H₁ receptors, but findings revealed that part of the anti-inflammatory effect of HQL-79 can be attributed to the inhibition of the conversion of PGH₂ to PGD₂ in mouse spleen extracts [58]. HQL-79 bonds to H-PGDS in a concentration-dependent manner [52]. Thus, HQL-79 can selectively suppress the production of PGD₂, unlike NSAIDs that can suppress cytoprotective and anti-inflammatory PGs. Moreover, it was reported that HQL-79 decreases urinary tetranor PGDM levels in mdx mice [60]. Urade et al. [59] found that HQL-79 suppressed muscular necrosis expansion in mouse models for DMD, and soon after new H-PGDS inhibitors were developed, which proved to be 100–3000 times more potent than HQL-79 [61]. Oral administration of these inhibitors decreased PGD₂ production and prevented skeletal muscle atrophy [61]. HPGDS inhibitors could be an effective therapy for DMD, but clinical trials are needed to further test these compounds, as well as their toxicity.

Cyclooxygenase (COX)-inhibiting NO donors (CINODs) are a group of compounds that display both the NO-donating moeity and the COX inhibitory activity with a single molecule. These compounds do not have the limitations of nitrate tolerance and hypotension associated with the organic nitrates use [62]. They were initially developed as alternatives to NSAIDs for the treatment of osteoarthritis, but recent CINOD treatments demonstrate beneficial effects in dystrophic mice, improving skeletal muscle flow, along with reducing inflammation and necrosis. HCT 1026, (an NO-donating flurbiprofen), and NCX 320, (an NO-donating ibuprofen) have been shown to reduce muscle necrosis and inflammation, and to have beneficial effects in preclinical models of muscular dystrophies [62-64]. HCT 1026 dramatically reversed functional muscle ischemia in mdx mice, and fully restored normal muscle blood flow [4]. Naproxinod, an NO-donating naproxen reduced the disease progression in mdx mouse subjects, and improved cardiac function. Moreover, naproxinod was assessed in adult patients with osteoarthritis [65], as well as in mdx mice subjects, showing increased resistance to fatigue in exercised mdx mice, improving the skeletal muscle strength, as well as reducing inflammation and fibrosis. Naproxinod is currently considered an optimal compound to be developed for treatment of DMD [62]. A recent study of Miglietta et al. compared naproxinod with naproxen in mdx mouse subjects, demonstrating that the additional anti-inflammatory activity of naproxinod is attributed to NO-donating moeity, and is not mediated by COX-inhibition [62]. With respect to the gastric damage caused by use of NSAIDs, naproxinod was shown to have milder effects on gastric mucosa, probably attributed to the NO protective effect [66]. Naproxinod is considered the most appropriate CINOD for pediatric application. The combined administration of isosorbide dinitrate (NO donor) with ibuprofen has shown a good safety profile and tolerability for long-term treatment, such as in DMD patients. In addition, patients receiving combined therapy (ibuprofen and isosorbide dinitrate) exhibited a significant and progressive reduction in serum TGF-β concentrations [67]. Sciorati et al. demonstrated that the same combined therapy was able to prevent alterations in left ventricular morphology of mdx mice [68]. This therapy reduced necrosis and muscle inflammation, and improved mouse performance in free wheel and treadmill tests. Soon after, another study demonstrated that the combination of isosorbide dinitrate and ibuprofen had optimal tolerability and safety profiles, and did not lead to pharmacokinetics interactions between two drugs [69]. In terms of therapeutic outcome and tolerability, CINODs proved to be more effective than corticosteroids, suggesting that CINODs are particularly important for patients with DMD with reduced levels and mislocalization of neuronal nitric oxide synthase μ (nNOSμ) from the sarcolemma in dystrophic muscle [70], secondary to dystrophin deficiency. NO is associated with muscle regeneration, increases in glucose uptake, blood flow and oxygen supply to contracting muscles, thereby contributing to greater resistance to fatigue [71].

Despite conflicting data concerning the role of LOX pathway in the
metabolism of muscle cells [40,72], findings from Gati I demonstrated that LOX inhibitors such as nordihydroguaiaretic acid (NDGA) could be beneficial in the treatment of muscular dystrophies [21]. NDGA blocked TNF-induced apoptosis in C3HA murine fibroblasts at one or more upstream points in the apoptotic pathway, causing mitochondrial inactivation, externalization of phosphatidyl serine and inhibition of caspase cleavage [21]. LOX inhibitors retard TNFα synthesis, exert an anti-apoptotic effect and stimulate production of prostaglandins, contributing to the survival of the myofibers [73,74]. However, leukotriene antagonists, and other LOX inhibitors should be tested in DMD patients to further confirm their beneficial effects. A comprehensive scheme of the above mentioned drugs, and other potential drugs, is reported in Table 1.

Considering that lipoxins or epi-lipoxins are pro-resolving molecules, they may provide new opportunities to design novel "resolution-targeted" therapies to control inflammation [75] and to develop new DMD drugs.

In summary, future research must focus on filling the gaps in the scientific literature regarding the role of LOX inhibitors, H-PGDS inhibitors, cyclooxygenase (COX)-inhibiting NO donors (CINODs), hybrid compounds targeting the pro-inflammatory AA mediators, or in other suitable interventions in the arachidonic acid pathway and mediators, necessary to modulate the inflammation by suppressing the pro-inflammatory arachidonic acid mediators and enhancing the anti-inflammatory arachidonic acid mediators, such as lipoxins, or epi-lipoxins. This great diversity in the treatment options by focusing on arachidonic acid pathway can encourage further studies in new anti-inflammatory compounds that can promote muscle healing and diminish inflammation in DMD patients.

Table 1

<table>
<thead>
<tr>
<th>Drug Categories</th>
<th>Name of drugs/potential drugs</th>
<th>Outcomes</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>H-PGDS inhibitors</td>
<td>4-benzhydrylxy-1-[3(1H-tetrazol-5-yl)-propyl]-piperidine (HQL-79) Other H-PGDS inhibitors more potent</td>
<td>PGIS inhibitors could be an effective therapy for DMD, but clinical trials are needed to further test this compound, as well as their toxicity</td>
<td>[Matushita et al. 1998], [Urade et al. 2006]</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Prednisone, Prednisolone, Deflazacort</td>
<td>They form the basis for the pharmacological treatment of Duchenne muscular dystrophy despite not being sufficiently effective.</td>
<td>[Bushby et al. 2010]</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Aspirin, Ibuprofen</td>
<td>Isometric tension did not differ in treated and untreated muscles with NSAIDs; however, resistance to fatigue decreased by treatment with aspirin and not with ibuprofen.</td>
<td>[Serra et al. 2012]</td>
</tr>
<tr>
<td>CINODs (Cyclooxygenase (COX)-inhibiting NO donors)</td>
<td>HCT 1026, NCX 320; Naproxinoid, Isoxproside dinitrate</td>
<td>Cyclooxygenase (COX)-inhibiting NO donors (CINODs) are a group of compounds that display both the NO-donating moiety and the COX inhibitor activity with a single molecule, that do not have the limitations of nitrate tolerance and hypotension, associated with the organic nitrates use.</td>
<td>[Baerwald et al. 2010], [Sciorti et al. 2013], [Miglietta et al. 2015], [Sciorti et al. 2011], [Brunelli et al. 2007], [Thomas et al. 2012]</td>
</tr>
<tr>
<td>LOX inhibitors</td>
<td>Nordihydroguaiaretic acid (NDGA)</td>
<td>NDGA can be beneficial in the treatment of muscular dystrophies. NDGA blocked TNF-induced apoptosis in C3HA murine fibroblasts at one or more upstream points in the apoptotic pathway, it caused mitochondrial inactivation, externalization of phosphatidyl serine, and inhibition of caspase cleavage.</td>
<td>[Gati et al. 2007]</td>
</tr>
</tbody>
</table>

1.3. Future perspectives

Considering the number of published reports in recent years, regarding the role of AA metabolites and of the agonists/antagonists of specific eicosanoid receptors, we suggest that it is necessary to conduct further studies to investigate different pathways that minimize inflammation in DMD patients, by targeting the AA metabolites.

The interplay between AA metabolites and DMD involves several mechanisms; these need to be taken into consideration when developing new compounds for patients with DMD. Whether these mechanisms are applicable to DMD patients remains to be determined. It is known that AA metabolites are involved in muscle fiber degeneration and regeneration. Although gene therapy is likely to be an efficient approach to cure DMD, inhibiting the pro-inflammatory AA metabolites or enhancing the anti-inflammatory AA metabolites, such as lipoxins released from the skeletal muscles of DMD patients, can be a potential strategy to alter the trajectory of disease. H-PGDS inhibitors, CINODs, iPLA2 inhibitors, LOX inhibitors, or hybrid compound with dual activities should be further assessed for their use in DMD patients. Also, the role of thromboxane A2 in DMD still need to be assessed. Despite the need to meet several criteria for an effective novel drug, such as having no toxicity, resolving the genetic defect, delaying the disease, and being economically affordable, we believe that future work in DMD will also address the role of AA metabolites.

To date, there is no clear image of the role of AA metabolites in DMD and the appropriate therapy. An urgent focus for further research is to identify possible interventions throughout the AA pathway and metabolites to modulate inflammation.

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