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Mechanisms of Zidovudine-Induced Mitochondrial Toxicity and Myopathy

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Key Words
Azidothymidine · Zidovudine · Skeletal muscle · Apoptosis · Oxidative stress

Abstract
Zidovudine (3-azido-3′-deoxythymidine), also referred to as azidothymidine (AZT), has become an integral component in highly active antiretroviral therapy, and has also been used in the treatment of cancer. The clinical effectiveness of AZT is constrained due to its association with increased adverse effects, such as myopathy. There are numerous potential mechanisms that may contribute to AZT-induced myopathy. The first hypothesized mechanism to explain AZT-induced toxicity was mtDNA depletion due to inhibition of DNA polymerase γ. Although mtDNA depletion is present in patients with myopathy, current data suggests that alternative mechanisms may play a more direct role in the myotoxicity. These mechanisms include AZT-induced oxidative stress, direct inhibition of mitochondrial bioenergetic machinery, and mitochondrial depletion of L-carnitine. Furthermore, we hypothesize that apoptosis may play a role in AZT-induced myopathy.

Introduction

Zidovudine (3-azido-3′-deoxythymidine), also referred to as azidothymidine (AZT), is a nucleoside analog reverse transcriptase inhibitor. The most common use of AZT has been in the treatment of AIDS as an integral component of highly active antiretroviral therapy. AZT is a powerful inhibitor of HIV replication. A synthetic thymidine analog compound, AZT undergoes intracellular triphosphorylation and inhibits viral replication by incorporating into the viral DNA strand, thus impeding the viral RNA-dependant DNA polymerase, also known as reverse transcriptase. AZT has also been used in the treatment of cancer. Most malignant cancers express telomerase, which has reverse transcriptase activity, and are therefore prone to the inhibitory effects of AZT.

Clinical effectiveness of AZT is constrained due to its association with increased adverse effects during chronic therapy at high doses. Included among the common adverse effects are hematological effects, such as anemia and neutropenia, hepatotoxicity, cardiomyopathy, and myopathy. Although it is known that myopathy is present in advanced HIV, it is important to acknowledge the association of myopathy with AZT therapy, including reports of the association at a rate around 17% [1]. Studies have indicated variable improvement rates in patients experiencing myopathy with AZT therapy when the medication was discontinued. Marked improvement or resolve of symptoms are noted in range of 18–100% of patients [2].

Patients with AZT-induced myopathy commonly complain of progressive generalized muscle pain, weakness, and fatigue. Patients often experience muscle atrophy and increased serum concentrations of creatine kinase, indicating muscle damage [3]. Ragged red fibers and structurally abnormal mitochondria are commonly

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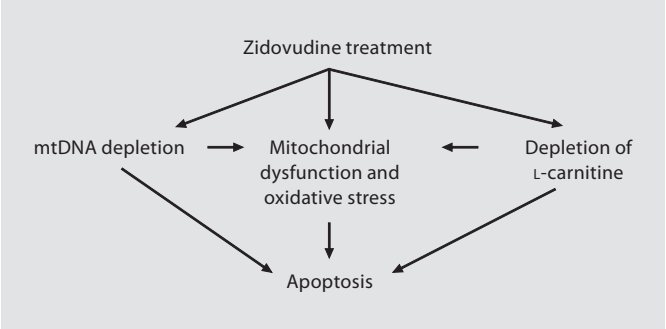

Fig. 1. Potential mechanisms of zidovudine-induced toxicity and myopathy. Zidovudine treatment can directly cause mtDNA depletion, mitochondrial dysfunction and oxidative stress, and a depletion of L-carnitine. The depletion of mtDNA and L-carnitine can also, in turn, induce mitochondrial dysfunction and oxidative stress. Each of these factors can lead to apoptosis.

present on biopsies [3]. It has been consistently shown that AZT therapy often causes mitochondrial DNA (mtDNA) depletion; however, the mechanism behind mtDNA depletion and its role in AZT-induced muscle toxicity has been recently debated.

Mechanisms of Zidovudine-Induced Myopathy

Several in vitro and in vivo studies have alluded to possible mechanisms leading to AZT-induced myopathy through the impairment of skeletal muscle mitochondria. Data suggest that the mechanism of mitochondrial toxicity due to AZT administration may be caused from mtDNA depletion, direct effects on mitochondrial bioenergetics, oxidative stress, reduced content of L-carnitine, and/or other mechanisms such as apoptosis (fig. 1).

mtDNA Depletion

It has long been hypothesized that the AZT-induced dysfunction of mitochondria is caused from the reduction of mtDNA content. Depletion of mtDNA has been reported in patients with AZT-related myopathy, and it also has been shown to be reversible by withdrawing the drug [2, 4, 5]. The 'mtDNA depletion hypothesis' infers that the depletion of mtDNA leads to dysfunctional complexes of the electron transport chain, thereby affecting oxidative phosphorylation and ATP production. Aerobic ATP production falls short of the minimum energy requirements necessary to maintain normal tissue and organ function, which leads to dysfunction. Furthermore, anaerobic glycolysis takes over to compensate for minimal energy, leading to a buildup of lactic acid [6, 7]. Indeed, it was shown that the AZT-induced depletion of mtDNA in blood cells preceded lactic acidemia in HIV infected patients [8].

It is currently debated whether AZT-induced mtDNA depletion may be due to inhibition of DNA polymerase γ or depletion of the mitochondrial pool of TTP (thymidine triphosphate). An understanding of AZT metabolism is necessary to delineate these mechanisms. AZT is first phosphorylated intracellulary by thymidine kinases to AZT triphosphate. In the triphosphorylated form, AZT and other nucleoside analogs compete with their natural substrates for HIV reverse transcriptase and DNA polymerase γ. As the triphosphorylated form of AZT is incorporated in the newly synthesized mtDNA strand during replication by DNA polymerase γ, chain termination ensues due to the lack of a 3′ OH group on the AZT molecule. It has been shown in vitro that AZT triphosphate can inhibit DNA polymerase γ; however, there is a lack of correlation between mtDNA depletion and DNA polymerase γ inhibition [9]. Furthermore, the concentration of AZT triphosphate has been reported to be undetectable in the mitochondrial matrix of mitochondria incubated with AZT [10]. Therefore, it is possible that the concentration of AZT triphosphate is inadequate to inhibit DNA polymerase γ. It has been shown that AZT inhibits the activity of thymidine kinases and, therefore, leads to depletion of the thymidine triphosphate pool necessary for mtDNA replication [10, 11]. By this mechanism, AZT would indirectly inhibit mtDNA replication and cause mtDNA depletion. It has been shown that symptoms of myopathy may be alleviated by uridine supplementation. Lebrecht et al. [12] report that supplementation of mitocnol, a dietary supplement with high uridine bioavailability, to zidovudine-treated mice attenuated all aspects of zidovudine-induced myopathy, including mtDNA depletion, mitochondrial bioenergetic abnormalities, and markers of oxidative stress. The mechanism of the beneficial effects of uridine supplementation is not fully delineated, but likely involves disinhibition of mtDNA replication by competing with zidovudine at some step of intracellular transport or phosphorylation or it may correct an intracellular pyrimidine deficit [12].

Mitochondrial Bioenergetics and Oxidative Stress

It has been suggested by others that the antiretroviral activity of AZT and the resulting mtDNA depletion may be distinct from the mechanism of mitochondrial toxic-

ity [13, 14]. AZT has been shown to inhibit the activity of a variety of enzymes involved in electron transport [13]. Dose-dependent inhibition of several enzymes of complex I and complex II were shown by AZT treatment of intact mitochondria taken from rat skeletal muscle [13]. It was also reported that AZT induced a loss of membrane potential, a reduction in ATP production, and a block in spontaneous contraction of myotubes in the absence of mtDNA depletion or deletions; the effects of AZT on mtDNA occurred at a later time point [15]. Yamaguchi et al. [14] also reported early cytotoxic effects of AZT, and showed AZT exposure in human lymphoid cells resulted in a decrease in ATP concentration and depletion of glutathione before mtDNA damage was detectable.

Depletion of glutathione occurs in conditions of oxidative stress, and therefore is suggestive that an increase in reactive oxygen species (ROS) production also occurs as an early event during AZT exposure. Glutathione is a cysteine tripeptide that is expressed in large quantities among eukaryotic cells. Its function is to eliminate ROS. As shown by Yamaguchi et al. [14], a decline in glutathione with the addition of AZT in vitro was seen as early as day 6 after the first exposure. By day 15 of exposure, glutathione levels ranged between 32 and 50% of the normal level. This decline was only after a small increase during days 3 and 5, indicating upregulation of the cytoplasmic redox control system with early treatment that led to deterioration after the retention period with the domination of ROS [14]. ROS can damage and alter the functions of DNA, proteins, and lipids; thus, leading to mitochondrial and cellular dysfunction. Additionally, it has been shown to interfere with muscular force production and to cause muscular fatigue. ROS production has not been directly measured in AZT-treated cells or isolated mitochondria; however, indirect evidence suggests that ROS may be involved in mitochondrial toxicity and myopathy. Skeletal muscle mitochondria of mice treated with AZT have a greater content of 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxo-dG), a marker of oxidative damage to DNA, and higher levels of oxidized glutathione than that of control mice [16]. Vitamin C and E treatment attenuated the AZT-induced oxidative damage and glutathione depletion. Wheeler et al. [17] have shown that AZT induces contractile dysfunction and muscular fatigue in the diaphragm of rats. Treatment with vitamin C and E prevented these AZT-induced muscular adverse effects. Furthermore, there is evidence that treatment with the mitochondrial antioxidant coenzyme Q10 may be beneficial in alleviating oxidative stress and symptoms of myopathy in both rats and humans [18, 19]. These data suggest that oxidative stress plays a role in AZT-induced myopathy. It is hypothesized that AZT may impair the electron transport chain causing an increased production of ROS and oxidative stress, which will eventually lead to a loss of the mtDNA integrity [14].

Reduced Mitochondrial Content of L-Carnitine

L-Carnitine, also known as levocarnitine, can be synthesized endogenously from the amino acids lysine and methionine, and gained exogenously with the ingestion of meats and dairy products. The main function of L-carnitine is to assist in the proper metabolism of long-chain fatty acids to energy by promoting their transport from the cytosol into the mitochondria for entry into β-oxidation. Muscle, among other organs and tissues, relies heavily on fatty acid oxidation for the production of energy. L-Carnitine is very prevalent in muscle tissue, accounting for 90–95% of the total amount of L-carnitine in the body.

There is a correlation between the accumulation of fatty acids within the muscle cell, due to inadequate fatty acid metabolism, and specific patients receiving treatment for AIDS with AZT [20]. The accumulation of lipid droplets in the cytoplasm of muscle cells may be due to mitochondrial dysfunction caused by mtDNA depletion and/or mitochondrial oxidative damage; however, evidence suggests that a reduction in the amount of cellular L-carnitine may be a major factor, and data show that AZT causes a reduction in cellular levels of L-carnitine [1, 20, 21]. Furthermore, treatment with L-carnitine attenuated the destructive effects of AZT on human myotubes; the volume and structure of mitochondria were preserved, and there was no accumulation of lipids with L-carnitine treatment [21]. Moreover, Georges et al. [1] showed that L-carnitine treatment of C2C12 cells, a myoblastic cell line, prevented the dose-dependent AZT-induced inhibition of cell growth. These data suggest that lipid accumulation is due to depletion of L-carnitine rather than mtDNA depletion or mitochondrial dysfunction.

Georges et al. [1] investigated the mechanism by which AZT treatment leads to cellular reduction in L-carnitine. It was shown that AZT reduces the transport of L-carnitine across the plasma membrane. AZT acts as a noncompetitive inhibitor of the sodium-dependent transport of L-carnitine. The data suggests that AZT may directly interact with the L-carnitine transporter.

Apoptosis

Apoptosis is a cell suicide program that is highly regulated and executed via activation of specific signaling pathways. Hence, particular morphological, biochemical, and molecular events occur, such as DNA fragmentation, nuclear condensation, and formation of apoptotic bodies which are then engulfed by macrophages or neighboring cells without initiating an inflammatory response. Apoptosis allows for the death of a single cell without death or disruption to the surrounding tissue. Apoptosis is mediated by activation of a variety of cysteine proteases, known as caspases. Caspases normally exist in an inactivated state called procaspases but can be activated by proteolytic cleavage and subsequent heterodimerization. Initiation of apoptosis involves activation of a caspase cascade in which 'initiator' caspases (i.e. caspase-8, caspase-9, caspase-12) first become activated and then cleave and activate 'effector' caspases (i.e. caspase-3, caspase-6, caspase-7). The effector caspases carry out the proteolytic events that result in cellular breakdown and demise. There are 14 known mammalian caspases (i.e. caspase-1 through caspase-14), which participate in the apoptotic process depending on the stimulus and respective signaling pathway activated and/or cell type undergoing apoptosis.

It is logical to hypothesize that apoptosis of muscle fibers may contribute to AZT-induced myopathy. The mitochondrion plays a central role in regulating apoptosis by releasing apoptogenic proteins, such as cytochrome *c*, into the cytosol initiating apoptotic signaling pathways in response to a stimulus. A variety of stimuli have been known to induce apoptosis, including many that are present in AZT-induced myopathy. Mitochondrial dysfunction, mtDNA mutations and depletion, oxidative stress, and accumulation of cellular fatty acids have all been shown to induce apoptosis in a variety of cell types [22–25]. Furthermore, several studies report prominent apoptosis in mitochondrial myopathies [26–29]. Apoptosis in skeletal muscle has also been documented to occur in cases of muscular dystrophy [30], chronic heart failure [31], cancer cachexia [32], skeletal muscle denervation [33], muscle unweighting [34] and with normal aging [35–37]. Apoptosis has also been implicated in statin-induced and steroid-induced myopathy [38, 39]. Hence, activation of apoptosis is a common phenomenon in pathophysiological skeletal muscle. Since AZT-induced myopathy resembles a type of mitochondrial myopathy, it may be likely that apoptosis plays a role in its progression.

AZT has been shown to induce apoptosis in a variety of cell types [40, 41]. The effects of AZT on human placental cells were studied since AZT is the drug of choice for preventing maternal-fetal HIV transmission [40]. It was reported that AZT induced mitochondrial ROS production and initiated apoptosis in a caspase-dependent manner in JEG-3 choriocarcinoma cells and primary explant cultures from term and first-trimester human placentas [40]. AZT also was shown to induce apoptosis in gastric cancer cells, with a strong positive correlation to the expression of caspase-3 mRNA and a negative correlation with the expression of Bcl-2 mRNA [42]. Bcl-2 is an anti-apoptotic protein that prevents the release of cytochrome *c* from the mitochondrion and, therefore, a decrease in expression of Bcl-2 would increase the apoptotic potential. AZT also was shown to induce apoptosis in human parathyroid cancer cells and human breast cancer cells in a dose-dependent manner [41, 43] and was also shown to radiosensitize human glioma cells [44]. AZT may contribute to cardiomyopathy by inducing apoptosis in cardiomyocytes [45]. Future studies will examine the effects of AZT-induced apoptosis in skeletal myocytes.

Conclusion

AZT causes numerous side effects, including myopathy. There are several potential mechanisms that may contribute to its myotoxicity. The first hypothesized mechanism to explain AZT-induced toxicity was mtDNA depletion due to inhibition of DNA polymerase γ. Although mtDNA depletion is present in patients with myopathy, current data suggests that alternative mechanisms may play a more direct role in the myotoxicity. These mechanisms include AZT-induced oxidative stress, direct inhibition of mitochondrial bioenergetic machinery, and mitochondrial depletion of L-carnitine. Although it has not been studied, it is likely that apoptosis may play a role in AZT-induced myopathy since AZT produces stimuli that have been shown to initiate the process of apoptosis. Future studies will elucidate this possibility.

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