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Review

The role of thiamine in HIV infection

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SUMMARY

Patients infected with HIV have a high prevalence of thiamine deficiency. Genetic studies have provided the opportunity to determine which proteins link thiamine to HIV pathology, i.e., renin–angiotensin system, poly(ADP-ribosyl) polymerase 1, Sp1 promoter gene, transcription factor p53, apoptotic factor caspase 3, and glycogen synthetase kinase 3β. Thiamine also affects HIV through non-genomic factors, i.e., matrix metalloproteinase, vascular endothelial growth factor, heme oxygenase 1, the prostaglandins, cyclooxygenase 2, reactive oxygen species, and nitric oxide. In conclusion, thiamine may benefit HIV patients, but further investigation of the role of thiamine in HIV infection is needed.

1. Introduction

Nutritional status has been related to disease development in patients infected with HIV. The dietary intake of vitamin C, thiamin, and niacin has been associated with a significantly slower progression to AIDS in homosexual men infected with HIV type 1.[1] Daily multivitamin use has been associated with a reduced risk of AIDS and a significantly reduced risk of low CD4 counts at baseline in HIV-positive homosexual men.[2] Taking multivitamin supplements during pregnancy improves weight gain and postnatal child growth, and reduces the risk of hypertension and adverse pregnancy outcomes in HIV-infected women.[3–6] Thiamine and vitamin B_6 supplements at more than twice the recommended dietary allowance have been associated with improved survival in HIV-infected patients.[7] Severe thiamine deficiencies, such as Wernicke encephalopathy and beriberi disease, are also observed in HIV patients.[8–11] Thiamine deficiency has been found in a large percentage of HIV-positive patients.[12–14] Long-term side effects, such as thiamine deficiency and lactic acidosis, have been found in HIV-infected patients using nucleoside reverse transcriptase inhibitors (NRTIs). Thiamine supplementation has been effective in treating NRTI-induced lactic acidosis.[15–19] Furthermore, treating *Schizosaccharomyces pombe* expressing HIV-1 viral protein R with a low concentration of hydrogen peroxide and 0.1 mmol/l thiamine significantly increased both the human cell proliferation and survival rates and decreased the number of elongated G_2-arrested cells.[20] Prosultiamine, a disulfide thiamine derivative, induced caspase-dependent apoptosis against human T-lymphotropic virus type 1 (HTLV-1) cells and significantly decreased the HTLV-1 proviral copy numbers to approximately 30–50% of their pretreatment levels in patients with HTLV-1-associated myelopathy/tropical spastic paruresis.[21] A trans-disulfide of thiamine disulfide suppresses HIV-1 replication by preventing the nuclear translocation of both HIV-1 Tat and nuclear factor kappaB (NF-κB).[22] Thiamine disulfide markedly inhibited the production of progeny HIV-1 in acutely and chronically HIV-1-infected cells.[23]

These results suggest a relationship between thiamine and HIV. Therefore, we review the role of thiamine in HIV infection.

2. Genetic factors related to thiamine in HIV

The primary function of the renin–angiotensin system (RAS) is to maintain fluid homeostasis and regulate blood pressure. Angiotensin-converting enzyme (ACE), a key enzyme in the RAS, converts angiotensin I to the potent vasoconstrictor angiotensin II.[24] Serum ACE levels have been found to be significantly elevated in AIDS patients, patients in the intermediate stage of HIV infection, and patients with *Pneumocystis carinii* pneumonia.[25,26] Captopril, an ACE inhibitor, may offer long-term renal survival benefits in HIV-associated nephropathy in animals and humans if the treatment is initiated prior to severe renal inefficiency.[27–29] An ACE inhibitor has also been shown to improve the mean velocity of circumferential fiber shortening and peak systolic left-ventricular wall stress in HIV-infected children.[30] HIV-positive patients who

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abuse cocaine have abnormalities in diastolic heart function and platelet activation that are potentially reversible with ACE inhibitor therapy.[31] Moreover, T-cell stimulation by HIV-1 gp160-derived peptide p18 (presented by HLA class I molecules in a cell-free system) has been found to require proteolytic cleavage, which is blocked by captopril.[32] An interaction between thiamine and the RAS has been observed. Thiamine deficiency significantly depresses plasma and urinary aldosterone responses to sodium deprivation in rats.[33] Thiamine attenuates hypertension and metabolic abnormalities in spontaneously hypertensive rats (SHRs). Thiamine repletion downregulates the expression of angiotensinogen (−80%), ACE (−77%), and angiotensin type 1 receptor (−72%) mRNAs in SHRs.[34] These observations suggest that thiamine affects ACE activity in HIV-infected patients.

Poly(ADP-ribosyl) polymerase 1 (PARP-1) is a nuclear protein present in mammalian cells and has been observed to regulate various biological activities. PARP-1 plays an important role in tissue injury in conditions associated with oxidative stress and inflammation. In HIV-infected cells, increased PARP-1 activity and accentuated fragmentation of cellular DNA are associated with HIV-1 replication.[35] In the brains of autopsied AIDS patients, immune-staining for PARP was found to be more intense in the gray and white matter of patients with HIV encephalitis.[36] PARP-1 is required for efficient HIV-1 integration; PARP-1 knockout fibroblasts were found to be nearly completely protected from HIV-1 infection.[37,38] Established small interference RNA (siRNA) against PARP-1 was found to significantly suppress HIV-1 replication, as well as the activation of the integrated HIV-1 long terminal repeat (LTR) promoter.[39] Thiamine has a cytoprotective effect on cultured neonatal rat cardiomyocytes under hypoxic insult; it also inhibits PARP cleavage and DNA fragmentation.[40] Benfotiamine, a fat-soluble thiamine analog, also prevents bacterial endotoxin-induced inflammation and PARP cleavage in mouse macrophage cell lines.[41] Adenosine thiamine triphosphate (ATTP), a new thiamine derivative, has been identified in small amounts in the mouse brain, heart, skeletal muscle, liver, and kidneys,[42] and has been shown to inhibit PARP-1 activity.[43]

Vpr is an HIV-1 virion protein that plays a role in enhancing HIV-1 replication in vivo. Vpr interacts with transcription factor Sp1 when Sp1 is bound to the Sp1 motifs within the HIV-1 LTR, and Vpr transactivation through Sp1 is critical for the immediate early transcription of HIV-1.[44] An interaction between NF-κB and Sp1 is required for inducible HIV-1 gene expression and may activate specific viral and cellular genes.[45] Sp1 and Sp3 regulate the basal transcription of the *ABOBEC3G* gene, which is expressed in peripheral blood lymphocytes and has activity against HIV-1 and other retroviruses.[46] Mutation of the Sp1 sequence impairs both multimerization and the membrane-binding activities of HIV-1 Gag.[47] Thiamine uptake in the human intestine occurs via a specialized carrier-mediated mechanism, and the human thiamine transporters (THTRs) are expressed in the intestine and are regulated via Sp1 promoter elements.[48,49]

The p53 gene and protein play critical roles in regulating the normal cell cycle, cell cycle arrest, and apoptosis. p53 expression and activation have been associated with faster disease progression in HIV-infected patients. Thakur et al.[50] provided evidence that the cell-killing effect of the HIV-1 viral protein Tat is mediated by activating the p53 pathway. In one experiment, p53 was fused with HIV Tat protein; the fusion product can cross cell membranes and influences HepG2 cell apoptosis.[51] The HIV-1-mediated increase in p53 gene expression is associated with the virus-mediated induction of type I interferon in human primary CD4 + T cells.[52] Tat contributes to neuronal degeneration by activating a pathway that involves the p53 and p73 transcription factors in neuroAIDS.[53] Activation of the p53-mediated pathways in the glia of HIV-associated dementia patients contributes to the neuroinflammatory processes that promote neurodegeneration by inhibiting glial proliferation and/or promoting glial cell dysfunction.[54] Vpr protein and transcript have been shown to be present in the brains of HIV-infected patients. Moreover, soluble Vpr caused neuronal apoptosis, cytochrome c extravasation, p53 induction, activation of caspase 9, and a depressive effect on the whole-cell currents in the neurons.[55] In contrast, an increased number of thiamine transporters are observed in cells that overexpress thiamine transport genes (mTHTR-1) and in cells that are exposed to conditions that induce DNA damage or p53 activation.[56] Thiamine diphosphate inhibits p53 binding, and thiamine inhibits intracellular p53 activity.[57] Thiamine treatment significantly decreases p53 expression in the cultured retinal neurons from diabetic rats.[58] These observations suggest that the pro-apoptotic transcription factor p53 is activated by cellular damage in HIV infection and that thiamine ameliorates these effects.

Caspases are cysteinyl aspartate-specific proteases that play a critical role in the regulatory and execution phases of apoptosis.[59] The overexpression of caspase 3 has been observed in the brains of pediatric patients with HIV-1 encephalitis.[60] The induction of apoptosis by HIV-1 envelope proteins gp120/160 in cultured endothelial cells is mediated by caspase 3 and cleavage of focal adhesion kinase in primary human CD4+ T cells.[61,62] HIV gp41-induced apoptosis is mediated by caspase 3-dependent mitochondrial depolarization, which is inhibited by the HIV protease inhibitor nelfinavir but not by other HIV protease inhibitors or inhibitors of calpain and cathepsin.[63] A potent and selective HIV-1 reverse transcriptase inhibitor, 3′-azido-2′,3′-deoxythymidine (AZT) is widely used in antiretroviral therapy. AZT inhibits visna/maedi virus-induced apoptosis and diminishes the activity of caspases 3, 8, and 9;[64] however, breast cancer cells that are transfected with the thiamine transporter *SLC19A3* gene show an increase in apoptosis when they are exposed to doxorubicin and radiation, and the caspase 3-dependent pathway partially mediates this effect.[65] The thiamine deficiency caused by thiamine antagonists leads to caspase 3 apoptosis in the neuronal differentiated PC-12 cells of rats.[66] Thiamine has a cytoprotective effect on cultured neonatal rat cardiomyocytes against hypoxia-induced apoptosis; it also inhibits caspase 3 activation.[40] Benfotiamine accelerates healing in the ischemic diabetic limbs of mice by potentiating angiogenesis and preventing the induction of pro-apoptotic caspase 3.[67] Sulbutiamine, a highly lipid-soluble synthetic analog of thiamine, attenuates trophic factor deprivation-induced cell death in transformed retinal ganglion cells (RGC-5) and decreases the expression of cleaved caspase 3.[68] These findings suggest that thiamine may influence HIV infection by inhibiting the activity of the apoptotic factor caspase 3.

Glycogen synthetase kinase 3β (GSK3β) is a protein kinase that is involved in many physiological processes, e.g., metabolism, gene expression, and apoptosis. The HIV-1 Tat-mediated activation of GSK3β contributes to Tat-mediated neurotoxicity[69] and antagonizes the NF-κB survival pathway in neurons.[70] GSK3β-specific inhibitors, such as AR-A014418 and B6B30, prevent direct neurotoxicity in primary human neurons exposed to HIV.[71] Exposure to pyrithiamine, an anti-thiamine compound, also increases the β-amyloid protein accumulation and GSK3 activity in the brain.[72] Benfotiamine was shown to improve cognitive function, reduce amyloid deposition, and suppress GSK3 activity in an animal model of Alzheimer's disease.[73] These findings suggest that thiamine may influence HIV by suppressing GSK3 activity.

3. The non-genetic role of thiamine in HIV

Matrix metalloproteinases (MMPs) are proteolytic enzymes that are responsible for extracellular matrix remodeling and for regulating of leukocyte migration through the extracellular matrix,