

The oxidative stress-induced niacin sink (OSINS) model for HIV pathogenesis

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Abstract:

Although several specific micronutrient deficiencies are associated with disease progression and increased mortality risk in HIV/AIDS, and even a simple multivitamin/mineral supplement can prolong survival, this is typically viewed merely as nutritional support of the immune system, and only necessary if there are deficiencies to be rectified. However, the reality is more complex. Several striking nutrient-related metabolic abnormalities have been consistently documented in HIV infection. One is chronic oxidative stress, including a drastic depletion of cysteine from the glutathione pool, and a progressive decline of serum selenium that is correlated with disease progression and mortality. Another is decreased blood levels of tryptophan, with an associated intracellular niacin deficiency. Tryptophan depletion or “deletion” by induction of indoleamine-2,3-dioxygenase (IDO), the first step in oxidative tryptophan metabolism, is a known mechanism for immune suppression that is of critical importance in cancer and pregnancy, and, potentially, in HIV/AIDS. Existing evidence supports the hypothesis that these nutrient-related metabolic abnormalities in HIV infection regarding antioxidants, selenium, sulfur, tryptophan and niacin are interrelated, because HIV-associated oxidative stress can induce niacin/NAD⁺ depletion via activation of poly(ADP-ribose) polymerase (PARP), which could lead to tryptophan oxidation for compensatory *de novo* niacin synthesis, thereby contributing to immune tolerance and T-cell loss via tryptophan deletion and PARP-induced cell death. This “oxidative stress-induced niacin sink” (OSINS) model provides a mechanism whereby the oxidative stress associated with HIV infection can contribute to immunosuppression via tryptophan deletion. This model is directly supported by evidence that antioxidants can counteract indoleamine-2,3-dioxygenase (IDO), providing the critical link between oxidative stress and tryptophan metabolism proposed here. The OSINS model can be used to guide the design of nutraceutical regimens that can effectively complement antiretroviral therapy for HIV/AIDS.

Keywords: Antioxidants | HIV-1 | Niacin | Nutraceutical | Nutrition | Oxidative stress | Tryptophan

Article:

1. Introduction: dietary factors, deficiencies and supplementation in HIV/AIDS

The use of vitamins, minerals, amino acids and other dietary supplements is widespread in HIV-infected populations, and not surprisingly, many such products are promoted as complementary-alternative medicine therapies by some supplement manufacturers and vendors, and aggressively marketed on the Internet. Unfortunately, but not unexpectedly, this has led to a backlash against the concept of HIV nutritional therapy in general.

Yet there is extensive evidence that certain micronutrient deficiencies are associated with faster disease progression or increased mortality risk, and that dietary supplements (e.g. a daily multivitamin) can prolong survival in HIV/AIDS (reviewed below). To establish the scientific basis of complementary nutritional therapies for HIV, there is an urgent need for mechanistic studies of promising nutraceutical compounds, and more evidence-based research to determine their potential for help or harm in HIV infection.

Numerous studies have demonstrated that the intake or blood levels of various micronutrients are significantly correlated with disease progression or outcome (i.e., survival vs. mortality) in HIV-1 infection (Abrams et al., 1993, Baum and Shor-Posner, 1998, Baum et al., 1997a, Baum et al., 1997b, Constans et al., 1995, Tang et al., 1993, Tang et al., 1996). These nutrients include B vitamins, antioxidant vitamins, zinc and selenium; similar correlations exist for nutrition-dependent biomolecules like the antioxidant glutathione, which requires the amino acid cysteine, which becomes depleted in HIV infection (Droge, 1993, Eck et al., 1989).

In countries where malnutrition is common, some studies document significantly lower levels of multiple trace minerals in HIV-infected subjects relative to uninfected controls, e.g., in Ethiopian HIV-infected pregnant women, deficiencies in zinc, magnesium, and selenium were found to be significantly greater than those in HIV-seronegative women, pregnant or otherwise (Kassu et al., 2008). In a recent Nigerian study, with the exception of zinc, all of the trace elements (Mg, Fe, Mn, Cu, Cr and Se) were significantly lower in HIV-infected patients compared to healthy controls (Olaniyi and Arinola, 2007). Such deficiencies in trace minerals can have far-reaching biochemical effects, given the ubiquitousness of metalloenzymes, but for the purposes of this review, one aspect stands out in importance: the potential relationship to oxidative stress. In addition to the antioxidant role of selenium in glutathione peroxidases, zinc, copper and manganese are essential components of the Cu/Zn and Mn superoxide dismutases, and zinc also plays roles in the repair of oxidant-induced DNA damage (Song et al., 2009).

Iron presents unique problems, because anemia is common in the developing world, suggesting a need for iron supplementation, yet elevated iron status is actually more dangerous in HIV infection, as it is a strong predictor of HIV-related mortality (McDermid et al., 2007). This is not surprising, as excess free iron can lead to increased production of superoxide and hydroxyl radical via the Fenton reaction; as will be discussed below, these molecular species can potentially contribute to HIV activation and pathogenesis.

As reviewed by Fawzi et al. (2005), various observational studies and randomized trials have shown that daily multivitamin supplements can reduce HIV disease progression and mortality (Fawzi et al., 2004, Jiamton et al., 2003, Kanter et al., 1999). As an example, in a Bangkok study reported in 2003, the participants, all HIV positive and not on antiretroviral drug therapy, were

given either a placebo or a daily multivitamin that included 400 mcg of selenium. The results showed a significant survival benefit for those taking the supplement, particularly for those who had the lowest CD4 cell counts; for study participants with a CD4 count under 100, those in the placebo group were 4 times as likely to die as those who were taking the supplement (Jiamton et al., 2003).

A study by Hurwitz et al. (2007) suggested that, in HIV+ subjects who were compliant, a daily supplement of 200 µg of selenium alone stopped progression of HIV-1 viral load increases, and led to improved CD4 counts. This is consistent with previous retrospective studies suggesting that, of all the nutrients studied, selenium stands out as a powerful predictor of outcome in HIV infection; in one study, selenium status was reported to be 10 times more significant than CD4 cell count as a predictor of mortality (Baum et al., 1997a). In another randomized, double-blinded, placebo-controlled trial, the co-administration of a trace mineral and antioxidant-rich supplement to patients on highly active antiretroviral therapy (HAART) led to significantly increased immune reconstitution at 12 weeks, as indicated by a 24% increase in absolute CD4 count in the micronutrient group, versus a 0% change in the (HAART-only) placebo group ($P = 0.01$); (Kaiser et al., 2006).

A comprehensive retrospective of the evidence for the role of nutritional factors in HIV disease pathogenesis and treatment is not my goal here, as there are already a number of recent reviews, some focused on specific nutrients or types of nutrients, and others looking at the broader spectrum of nutrition in HIV/AIDS (Allard et al., 1998, Baum, 2000, Baum and Shor-Posner, 1998, Coodley et al., 1993, Drain et al., 2007, Fawzi et al., 2005, Lanzillotti and Tang, 2005, Patrick, 1999, Singhal and Austin, 2002, Tang et al., 1996, Taylor et al., 2000).

The conventional viewpoint is that dietary supplementation is beneficial in HIV infection simply because certain micronutrients are particularly important for proper functioning of the immune system. However, the situation is much more complex. In this article, I will focus on several underlying metabolic nutrient-related abnormalities, to be presented below, that have been well documented in HIV infection, at both the cellular and systemic levels. A review of the literature suggests that certain key biochemical pathways of amino acid and micronutrient metabolism may play critical roles in producing or mediating these abnormalities, thus contributing to HIV pathogenesis. An understanding of the mechanisms involved is desirable for the optimization of nutrition-based complementary therapies, which also has the potential to permit the use of lower and less toxic doses of antiretroviral drugs, due to synergy of combined nutritional and drug therapies. The latter can be quite dramatic, e.g. as in the case of resveratrol and anti-HIV nucleosides (Heredia et al., 2000).

2. Underlying mechanisms of nutrient-related metabolic abnormalities in HIV infection

There are four biochemical systems or pathways of primary interest, and their interactions are illustrated in a simplified schematic diagram shown as Fig. 1. The significance of each of these biochemical systems in HIV disease will be briefly reviewed in subsequent subsections. These four systems include:

- Redox status and antioxidant defenses, particularly as linked to sulfur (cysteine, glutathione) and selenium biochemistry;
- Tryptophan metabolism, now understood to be a key immune regulatory system, with the potential to induce immune tolerance (e.g. to the fetus in pregnancy) and immunosuppression (Mellor et al., 2002, Mellor et al., 2003, Murray, 2003);
- Arginine metabolism, which via nitric oxide (NO) and peroxynitrite production contributes to free radical biochemistry and thus interacts intimately with the antioxidant defense system, and which has also recently emerged as a critical biochemical pathway in the regulation of inflammation and immunity (Bansal and Ochoa, 2003, Brito et al., 1999, Bronte et al., 2003, Bronte and Zanovello, 2005, Mills, 2001);
- The poly(ADP-ribose) polymerase (PARP) complex, which can induce niacin/NAD⁺ depletion via its activation under oxidative stress (Cookson et al., 1998, Koh et al., 2005, Tronov and Konstantinov, 2000, Virag, 2005), and thus is a point of intersection of the first three systems (see Fig. 1 and subsequent discussions for a full explanation).

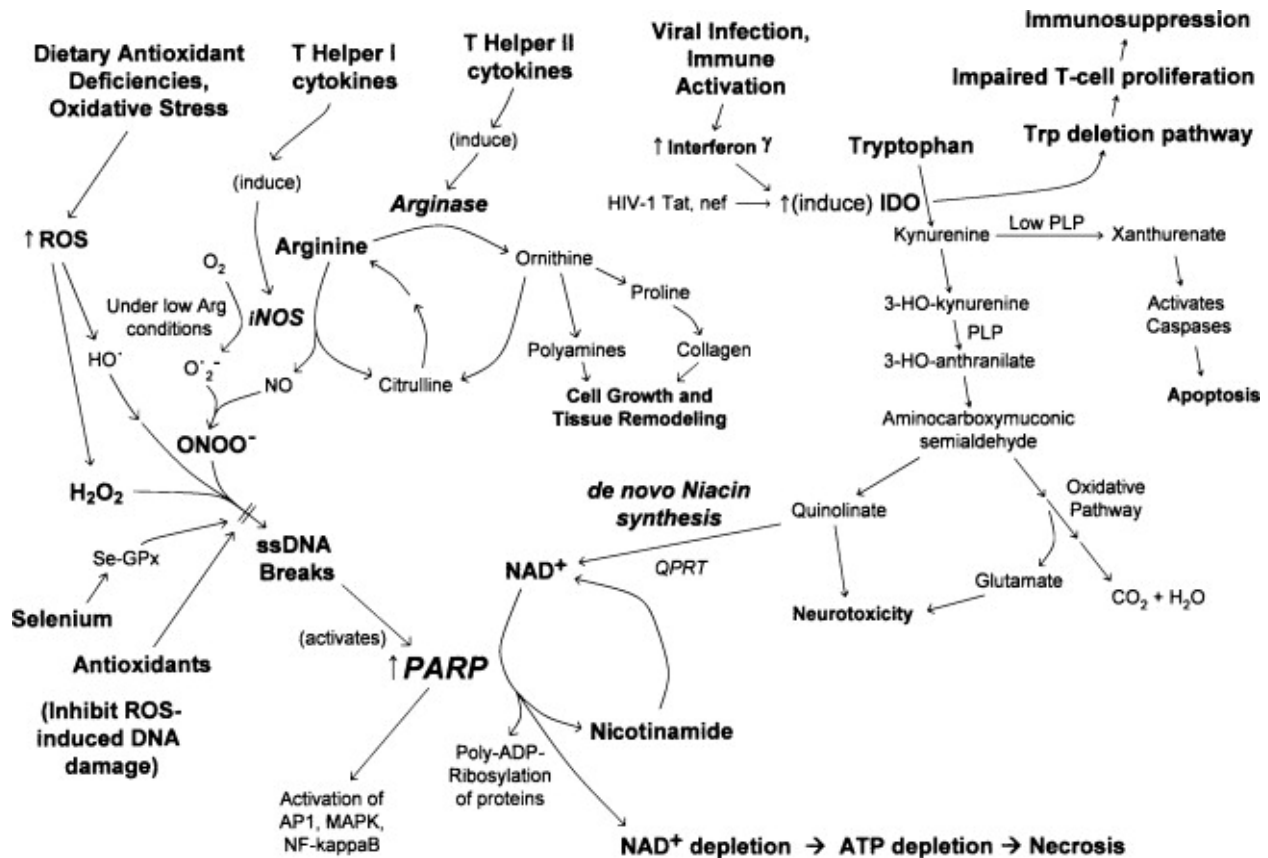


Figure 1. Illustration of the molecular basis of a link between four biochemical pathways involved in HIV-induced metabolic abnormalities: (1) antioxidants (Se, GPx, GSH) vs. ROS mediated oxidative stress (left); (2) tryptophan oxidation via the indoleamine-2,3-dioxygenase (IDO) pathway leading to immunosuppression by tryptophan deletion (right); (3) arginine metabolism, increased under cytokine induction of both iNOS and arginase, leading to increased peroxynitrite formation under arginine-limited conditions, and (4) the poly(ADP-ribose) polymerase (PARP) complex, which when activated by oxidative stress can induce niacin/NAD⁺ depletion, creating a demand for *de novo* niacin synthesis from tryptophan. This illustrates a potential mechanism whereby oxidative stress associated with HIV infection can contribute to immunosuppression by tryptophan deletion, and also to T-cell loss via PARP-induced necrosis and/or apoptosis.

The clinically manifested HIV-associated nutrient-related metabolic abnormalities to which the above biochemical pathways contribute can be grouped into two major categories, as described in Sections 2.1 Chronic oxidative stress, sulfur metabolism and selenium deficiency in HIV/AIDS, 2.2 Tryptophan depletion in HIV infection: immunosuppression induced by tryptophan metabolism and its role in below.

2.1. Chronic oxidative stress, sulfur metabolism and selenium deficiency in HIV/AIDS

2.1.1. Selenium

Probably the earliest noted antioxidant defect in HIV-infected patients was the apparent progressive decline in blood levels of the essential dietary antioxidant selenium (Se) that was first reported by Dworkin in the mid-1980s (Dworkin et al., 1985, Dworkin et al., 1986). This decline has been widely documented in many independent studies, as reviewed (Baum and Shor-Posner, 1998, Campa et al., 2000, Constans et al., 1999, Taylor et al., 1997), and was generally found to be more severe in full-blown AIDS patients (Dworkin et al., 1988). This effect is even more pronounced during co-infection with hepatitis C virus (Look et al., 1997). Various retrospective studies demonstrated a correlation between serum selenium concentration and CD4 T-cell counts (e.g., Beck et al., 1990, Look et al., 1997). Low serum selenium was eventually shown to be highly correlated with disease progression and increased mortality risk (e.g., Baum et al., 1997a, Campa et al., 1999, Constans et al., 1995).

2.1.2. Sulfur

HIV infection is typically characterized by a dramatic decline in glutathione levels, even in asymptomatic individuals, first shown in the late 1980s (Buhl et al., 1989, Look et al., 1997). This is associated with an “alarming” negative sulfur balance (Breitkreutz et al., 2000), i.e., depletion of cysteine largely from the glutathione (GSH) pool, and its excretion as sulfate, contributing to the AIDS wasting syndrome (Breitkreutz et al., 2000, Droge et al., 1988, Droge et al., 1994, Eck et al., 1989). Note that this suggests an abnormal degree of biological oxidation, manifesting as elimination of cysteine sulfur as sulfate.

A key feature of HIV disease is an apparent “antioxidant defect”, as proposed by Favier et al. (1994), which provides a novel perspective for understanding the role of many oxidative stress-inducing cofactors that are known to accelerate the progression of AIDS. HIV infection can be aggravated by cofactors such as malnutrition, co-infection with other microorganisms, and the use of various oxidant drugs, such as nitrites.

2.2. Tryptophan depletion in HIV infection: immunosuppression induced by tryptophan metabolism and its role in *de novo* niacin (NAD⁺) synthesis

Significantly decreased blood levels of the essential amino acid tryptophan in infected individuals were noted fairly early on in the HIV epidemic (Larsson et al., 1989, Werner et al., 1988). Confirming those early reports, a 2003 survey of the data from 16 published studies suggested that, despite adequate dietary intake, the average tryptophan blood level in HIV infection is almost 30% below that of normal uninfected individuals (Murray, 2003). This has

been unambiguously attributed to increased oxidation of tryptophan, one outcome of which leads to the *de novo* synthesis of nicotinamide adenine dinucleotide (NAD⁺), a form of vitamin B3, niacin. This is a long and inefficient synthesis, which requires pyridoxal phosphate (PLP, the active form of vitamin B6) at the third step. Under normal conditions of health, typically less than 2% of dietary tryptophan is converted to NAD⁺ by this pathway (Murray, 2003).

Intermediates of oxidative tryptophan metabolism have also been implicated in neurotoxicity, potentially contributing to AIDS dementia (Heyes et al., 1992). These include glutamate, quinolinic acid and xanthurenic acid, which is produced from kynurenine under conditions of inadequate vitamin B6, and has been shown to be a pro-apoptotic molecule (Malina et al., 2001).

The phenomenon of tryptophan oxidation is of particular significance for the immunodeficiency associated with HIV infection, because in other contexts, a local deficit of tryptophan resulting from tryptophan oxidation impairs T-cell function, leading to immunological tolerance; this has been called “immunosuppression by starvation” (Mellor and Munn, 1999). This is exploited by the maternal immune system to induce fetal tolerance during pregnancy. Mellor and Munn have published a series of studies (Mellor et al., 2002, Mellor and Munn, 1999, Mellor and Munn, 2001, Munn et al., 1999) elucidating the mechanism whereby induction of oxidative metabolism of tryptophan in certain immune cells (e.g., macrophages and dendritic cells) appears to trigger cell cycle arrest in nearby lymphocytes, preventing T-cell proliferation, leading to immune tolerance of the fetus. They call this immunosuppression by starvation, because they hypothesize that “tryptophan deletion” is the underlying mechanism (Mellor and Munn, 1999, Murray, 2003). Thus, tryptophan deletion in HIV infection would also be expected to contribute to immunosuppression.

Tryptophan deletion via induction of IDO by the Th1 cytokine interferon- γ can also be used by the immune system to starve a pathogen — this is well established in the case of certain nonviral intracellular pathogens, e.g. *Toxoplasma gondii*, as reviewed by Murray (2003). In the case of HIV-1, the viral proteins tat and nef have been shown to induce IDO, possibly contributing to the tryptophan depletion observed in AIDS. The possibility that this is a deliberate viral strategy contributing to immunosuppression has been suggested (Murray, 2003).

Paradoxically, despite the increased metabolism of tryptophan during HIV infection (Larsson et al., 1989, Werner et al., 1988), which could result in increased niacin synthesis, there is an associated intracellular deficiency of niacin, i.e. NAD⁺ (Brown et al., 1991), creating a state of “intracellular pellagra” (Murray et al., 1995), the induction of which may involve both virus and host factors (Murray, 2003).

A pilot study by Murray et al. (2001) clearly demonstrated that the reduction in serum tryptophan levels induced by HIV infection can be countered by high-dose niacin supplementation. Presumably, correction of the state of “intracellular pellagra” leads to decreased demand for tryptophan oxidation for *de novo* NAD⁺ synthesis (Murray, 1999). It is also possible that the high doses of nicotinamide used in this study could lead to inhibition of PARP, thus further reducing NAD⁺ depletion and the need for tryptophan oxidation.

2.3. Biological oxidation as a common factor

Note that excessive oxidation is a common factor in all of the above:

- Selenium deficiency or depletion leads to impaired glutathione function and oxidative stress, which is also increased by viral infection and cytokine activation (see below);
- This can contribute to depletion of glutathione via oxidation of its key component cysteine to sulfate, leading to negative sulfur balance;
- Oxidation of tryptophan is the first step in the tryptophan deletion pathway, which can directly contribute to immunosuppression, and,
- Finally, the tryptophan deletion seen in HIV infection can be seen in part as a compensatory response to niacin depletion resulting from oxidative stress (explained below; remember that tryptophan oxidation is the first step in the *de novo* niacin synthesis pathway, an extremely inefficient biosynthesis that is required when niacin levels are inadequate).

3. Other biochemical pathways contributing to or linking oxidative stress and tryptophan metabolism

3.1. Arginine metabolism, peroxynitrite, and regulation of T-cell proliferation and apoptosis

Arginine metabolism contributes to many important areas of biochemistry and physiology, such as regulation of vascular tone via the role of NO as the endothelial relaxing factor. The discussion here will be limited to two of its most important metabolizing enzymes, arginase and nitric oxide synthase (NOS), which are key components of an important immune regulatory system that has only been fully elucidated since 2000 (Bansal and Ochoa, 2003, Bronte et al., 2003, Bronte and Zanovello, 2005, Mills, 2001). As illustrated in Fig. 1, iNOS (as well as its other NOS isoforms) converts arginine to citrulline and NO; this is in competition with arginase, which converts arginine to urea and ornithine, which can further be converted into proline or polyamines, both of which are important for growth and tissue remodeling; thus arginase is induced in trauma and other states where tissue healing is required (Bansal and Ochoa, 2003, Witte and Barbul, 2003). Extracellularly released arginase from granulocytes can induce profound suppression of T-cell proliferation (Munder et al., 2006), an effect which is also observed during pregnancy (Kropf et al., 2007). Arginase activity is significantly increased in the peripheral blood and placenta of pregnant women, leading to decreased placental arginine levels, and impaired T-cell functions (Kropf et al., 2007). This has striking similarities to the role of tryptophan metabolism in pregnancy.

Since about 1995, it has been known that the NOS/arginase balance is under reciprocal regulation of Th1 and Th2 cytokines, with Th1 cytokines like TNF- α and interferon- γ being inducers of NOS, whereas Th2 cytokines like IL-4 and IL-10 inhibit NOS expression, and are potent inducers of arginase (Bronte et al., 2003, Modolell et al., 1995, Munder et al., 1998, Munder et al., 1999).

When both arginase and NOS2 (inducible NOS, iNOS) are induced (e.g., during inflammation), competition for arginine as a substrate leads to arginine depletion (Bronte et al., 2003). Under these arginine-limited conditions, synthesis of the reactive oxygen species (ROS) superoxide and

peroxynitrite increases, which is counterintuitive, because production of NO, the precursor for peroxynitrite, will be diminished. Increased production of peroxynitrite by NOS under low arginine conditions has now been established for all three isoforms of NOS (Forstermann, 2006, Xia et al., 1996, Xia and Zweier, 1997). As shown in Fig. 1, when inadequate arginine is available as substrate, the excess electrons generated by NOS are passed to oxygen to form superoxide, $O_2^{\bullet -}$ (Forstermann, 2006, Pou et al., 1992, Pou et al., 1999). Rapid combination of this superoxide with the NO that is formed from available arginine by the same enzyme results in the conversion of NOS into a machine for efficient production of peroxynitrite (Xia et al., 1996, Xia and Zweier, 1997), as seen in Fig. 1. This can result in peroxynitrite mediated cell injury (Xia et al., 1996), particularly in inflammatory diseases like asthma (Meurs et al., 2003, Ricciardolo et al., 2005).

In the immune system, under the direction of Th1 and Th2 cytokines (Bronte et al., 2003), this arginine-based mechanism is used to regulate T-cell proliferation and apoptosis. Specifically, peroxynitrite generated under arginine-limited conditions acts to inhibit T-cell activation and proliferation (Brito et al., 1999), and can cause activated T-cells to undergo apoptosis (Brito et al., 1999, Bronte et al., 2003, Bronte and Zanovello, 2005). This consequence of arginine depletion is a direct threat to HIV, which preferentially replicates in activated cells.

A critical role for arginine in HIV infection is supported by extensive evidence that arginine is of importance for both innate and acquired immune mechanisms (Bansal and Ochoa, 2003, Bronte et al., 2003, Bronte and Zanovello, 2005, De Santo et al., 2005, Mills, 2001). A role for NO in HIV pathogenesis is also well documented (Blond et al., 2000, Jimenez et al., 2001, Mannick et al., 1999, Mossalayi et al., 1999, Persichini et al., 1999, Torre et al., 2002). But peroxynitrite ($ONOO^-$), not NO per se, is probably the key mediator in this case (Fig. 1).

3.2. The poly(ADP-ribose) polymerase (PARP) complex is at the intersection of these systems

The link between tryptophan depletion in HIV infection and the underlying antioxidant defects of selenium and sulfur/cysteine/glutathione is that oxidative stress can induce niacin/NAD⁺ depletion (Grant et al., 2000, Rawling et al., 1994). The mechanism by which oxidative stress leads to niacin depletion involves a cellular defense enzyme called the poly(ADP-ribose) polymerase (PARP), which is activated by oxidative damage to DNA (Cookson et al., 1998, Virag, 2005, Virag and Szabo, 2002). When a cell is oxidatively damaged beyond repair, PARP kicks into high gear to burn up (polymerize) all the intracellular NAD⁺, which leads to cell death via exhaustion of ATP.

PARP detects single-stranded DNA breaks, triggering the transfer and polymerization of ADP-ribose from NAD⁺ onto more than 40 nuclear proteins, particularly histones, certain transcription factors including NF- κ B, and PARP itself, modulating their activities and functions. Activated by DNA breaks, PARP facilitates transcription, replication, and DNA base excision repair (Virag and Szabo, 2002). Because hydrogen peroxide and peroxynitrite in particular are highly effective in producing single-stranded breaks in DNA, oxidative stress is a potent inducer of PARP, therefore capable of inducing niacin/NAD⁺ depletion (Cookson et al., 1998, Koh et al., 2005, Tronov and Konstantinov, 2000, Virag, 2005). Thus, PARP is a point of intersection of the three biochemical systems or pathways described in Sections 2.1 Chronic oxidative stress, sulfur

metabolism and selenium deficiency in HIV/AIDS, 2.2 Tryptophan depletion in HIV infection: immunosuppression induced by tryptophan metabolism and its role in, 3.1 Arginine metabolism, peroxynitrite, and regulation of T-cell proliferation and apoptosis (see Fig. 1 for a graphical illustration of this concept).

4. The oxidative stress-induced niacin sink (OSINS) model for HIV pathogenesis

Data reviewed in the previous section show how reactive oxygen species (ROS, e.g., peroxynitrite and peroxide), which increase under deficiency of arginine and selenium respectively, can cause NAD⁺/niacin depletion via DNA damage and PARP activation. The most important single idea of this article is that this can potentially lead to tryptophan oxidation for compensatory niacin synthesis. The resulting tryptophan deletion can then contribute to immunosuppression by established mechanisms, as reviewed in Section 2.2 (Mellor and Munn, 1999, Moffett and Namboodiri, 2003, Murray, 2003), and also to T-cell loss via PARP-induced necrosis or apoptosis (Cookson et al., 1998, Koh et al., 2005, Tronov and Konstantinov, 2000).

A role for oxidative stress can also explain the paradox of why there is an associated intracellular deficiency of niacin in HIV-infected cells, despite the increased metabolism of tryptophan, which should result in increased niacin synthesis. Oxidative stress creates a niacin “sink” that depletes both niacin and tryptophan.

Thus, the oxidative stress-induced niacin sink (OSINS) model (Fig. 1) simply states that niacin/NAD depletion (requiring *de novo* synthesis from tryptophan) links oxidative stress and selenium to the observed tryptophan abnormalities and immunosuppression in HIV/AIDS. The OSINS model provides a mechanism whereby oxidative stress associated with HIV infection can contribute to immunosuppression via tryptophan deletion, as well as neurotoxicity via toxic tryptophan metabolites and ATP depletion.

The process of viral infection itself, and inflammatory aspects of the immune response, are potential contributors to the oxidative stress seen in HIV infection (Israel and Gougerot-Pocidalo, 1997, Valyi-Nagy and Dermody, 2005). Cytokine release and viral proteins like HIV env, tat and nef, have all been found to have pro-oxidant effects. But whatever the source of oxidative stress, there would be a net effect towards niacin depletion and compensatory tryptophan oxidation, with PARP activation as the primary link.

5. Significance for the design of nutrient-based regimens as complementary therapies for HIV

An important point of this analysis is to show that the need for certain nutrients in HIV infection may be largely secondary to an underlying defect that could be largely rectified by another nutrient, with antioxidants being the most fundamental to an effective regimen. Thus, in pilot studies in HIV-infected populations:

- Supplementation with selenium alone has been shown to significantly restore glutathione levels (Delmas-Beauvieux et al., 1996), and a combined antioxidant supplement devoid

of sulfur content still produced significant increases in glutathione (Batterham et al., 2001).

- In HIV-infected individuals, supplementation with niacinamide has been shown to lead to a 40% increase in serum tryptophan levels that were previously deficient, without any tryptophan supplementation (Murray et al., 2001). Presumably, correction of the state of “intracellular pellagra” leads to decreased demand for tryptophan oxidation for *de novo* niacin synthesis (Murray, 1999).

Similarly, it is expected that supplementation with antioxidants should at least partially rectify the state of intracellular pellagra and tryptophan deficiency induced by HIV infection. Furthermore, there may be some combination of nutrients (e.g., inclusion of niacin along with antioxidants) that will act synergistically to reverse these infection-induced metabolic abnormalities.

It is a specific prediction of the OSINS model that antioxidants should downregulate, inhibit or counteract IDO, since antioxidants will block PARP activation (i.e., act to plug the niacin “drain”), so that less compensatory niacin synthesis (via induction of IDO) would be required. There is at least one study that clearly demonstrates this, although the authors never mention PARP or the concept of compensatory niacin synthesis. Thomas et al. (2001) showed that IDO was inhibited by the antioxidant pyrrolidine dithiocarbamate, via a post-translational mechanism.

6. Conclusions and significance

An extensive body of evidence shows that certain nutrient deficiencies are associated with faster disease progression or increased mortality risk, and pilot studies suggest that micronutrient supplements (e.g. a daily multivitamin-mineral) can prolong survival in HIV/AIDS. Hence, there is a critical need to elucidate the cellular and viral mechanisms involved, with the aim of providing theoretical and empirical foundations for future clinical trials and supplementation programs involving micronutrients, amino acids and antioxidants as complementary therapies for HIV/AIDS. Such studies and programs would be highly relevant to a majority of the populations most affected by the HIV/AIDS pandemic, including

- HIV+ populations in the developing world where sub-optimal nutrition is common,
- Pediatric populations, which are more susceptible to the toxic side effects of antiretroviral therapy,
- HIV+ pregnant women, because HIV infection can be exacerbated by the immunosuppression that is induced in pregnancy to avoid fetal rejection, via induction of tryptophan oxidation (Mellor et al., 2002) and arginine metabolism by the enzyme arginase (Kropf et al., 2007),
- Drug abusing populations, which often manifest multiple nutritional deficiencies, as well as drug-induced oxidative stress, as reviewed by Taylor et al. (2000);
- HIV-infected persons worldwide experiencing CNS infection, because antiretroviral drugs have limited ability to penetrate the blood-brain barrier (McGee et al., 2006), so nutritional therapies represent an alternative approach to diminishing the impact of HIV-associated metabolic abnormalities in the brain.

I have reviewed a body of evidence which shows that several underlying metabolic nutrient-related abnormalities are present at both the cellular and systemic level, at least in untreated HIV infection (Sections 2.1 Chronic oxidative stress, sulfur metabolism and selenium deficiency in HIV/AIDS, 2.2 Tryptophan depletion in HIV infection: immunosuppression induced by tryptophan metabolism and its role in). Certain key biochemical pathways of amino acid and antioxidant micronutrient metabolism play critical roles in producing or mediating these abnormalities, thus contributing to HIV pathogenesis (Sections 3 Other biochemical pathways contributing to or linking oxidative stress and tryptophan metabolism, 4 The oxidative stress-induced niacin sink (OSINS) model for HIV pathogenesis).

The OSINS model provides a framework that could be a starting point for a systems biology approach to the discovery and optimization of “combination” nutraceutical therapies for HIV infection. The essence of the OSINS model is that, via DNA damage and PARP activation, whatever underlies or contributes to the antioxidant defect and increased oxidative stress associated with HIV infection, leads also to intracellular niacin depletion, and thereby to tryptophan depletion, with an end result of immunosuppression (Mellor and Munn, 1999, Moffett and Namboodiri, 2003, Murray, 2003), and also T-cell loss via PARP-induced cell death (Cookson et al., 1998, Koh et al., 2005, Tronov and Konstantinov, 2000). Since immunosuppression is the defining feature of HIV disease, this has the potential to be a fundamental mechanism of HIV pathogenesis.

Hopefully, this analysis of the underlying mechanisms of action of nutrients, their deficiencies and their interactions in HIV infection may help to provide a rational basis for the design of clinical trials of micronutrients, amino acids and antioxidants as complementary therapies for HIV/AIDS.

Conflict of interest statement

None.

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