Tryptophan depletion and HIV infection: a metabolic link to pathogenesis

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HIV-1-infected patients have low circulating tryptophan concentrations despite evidence of adequate dietary intake of this essential aminoacid. A chronic increase in inducible tryptophan oxidation is the basis of HIV-1-associated tryptophan depletion. This metabolic process results in the irretrievable loss of tryptophan molecules from the available pool. Such sustained disruption of normal tryptophan metabolism over time disturbs the many metabolic processes involving this aminoacid, and has been implicated in some features of AIDS pathogenesis. Normal T-cell function is adversely affected by tryptophan depletion, but the extent of the effect in HIV-1-infected patients is still unclear. Attempting to directly supplement tryptophan is not advised given the potential increase in circulating concentrations of neurotoxic intermediates. Although only preliminary data are available, evidence suggests that antiretroviral and nicotinamide treatments can boost plasma tryptophan concentrations in HIV-1-infected patients and impact the secondary effects of tryptophan depletion. Additional study of this metabolism could lead to improved treatment strategies for patients with HIV infection. In this review I focus on the potential links between disturbed tryptophan metabolism and pathogenesis.

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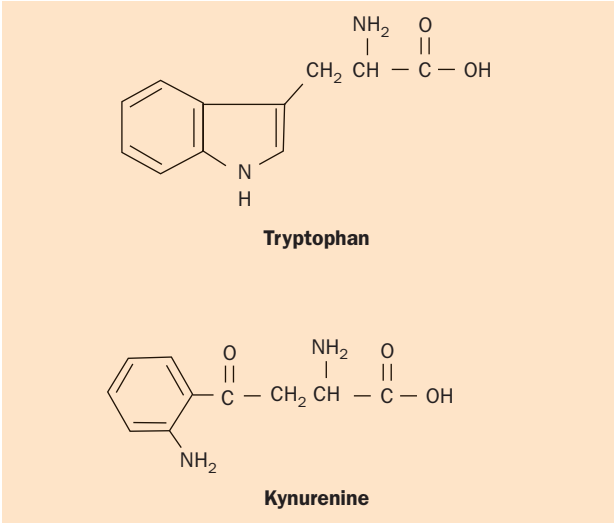

Figure 1. The structures of tryptophan and kynurenine. The first step in the major oxidative pathway of tryptophan is the conversion of tryptophan to kynurenine. This process involves the cleavage of the five-membered indole ring. Cleavage is done by L-tryptophan 2,3-dioxygenase in the liver and indolamine 2,3-dioxygenase in the periphery. Once cleaved, the indole ring cannot be resynthesised by human metabolism; any additionally required tryptophan must be obtained via dietary intake.

Human beings cannot synthesise the indole ring of tryptophan (figure 1). The body's supply of tryptophan, therefore, must be obtained from the environment in the preformed state. This dietary requirement places tryptophan in the group of essential aminoacids. The required minimum daily intake for tryptophan is 175 mg daily for adult women and 250 mg daily for adult men.[1] The average diet in developed countries far exceeds this requirement, generally including about 1 g tryptophan daily.[2] Circulating concentrations of plasma tryptophan come from two sources: newly acquired dietary tryptophan, and tryptophan that has been released for recycling during protein turnover.[3] HIV-1-infected individuals have no consistent dietary deficiency in proteins or aminoacids,[4] yet the plasma of patients with asymptomatic early disease and those with more advanced disease have a reproducible pattern of tryptophan depletion at all stages of infection (table 1).[3–18] This depletion of tryptophan deepens with advancing disease,[16] and contributes to HIV pathogenesis.

L-Tryptophan 2,3-dioxygenase (TDO) is the liver-specific enzyme that does most tryptophan oxidation via indole-ring cleavage during periods of homoeostasis (figure 2A). Because of the high Km of TDO, it has notable activity only when tryptophan concentrations exceed basal requirements for protein and serotonin synthesis.[3] Tryptophan, like other aminoacids, can be oxidised to generate energy. Excess dietary tryptophan is routinely metabolised via this major oxidation pathway to produce ATP, carbon dioxide, and water in healthy adults. A side product of this metabolism is the production of niacin (ie, nicotinamide and nicotinic acid); in fact, the basal activity of this pathway transforms around 2% of dietary tryptophan molecules to niacin (figure 3). When tryptophan overload is experimentally induced (tryptophan load testing), up to 99% of the tryptophan is oxidised via TDO.[19]

Inducible tryptophan oxidation can be initiated extrahepatically via a second enzyme, indolamine 2,3-dioxygenase (IDO). IDO was first isolated from rabbit intestine, and its in-vitro activity extends to indole-

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containing compounds other than tryptophan.[20] This enzyme is expressed in several cells, including macrophages, dendritic cells, and placental trophoblasts. It has been implicated in the overactivation of tryptophan catabolism in HIV-1 infection. Tryptophan concentrations were diminished by an average of 28·5% compared with controls (table 1).[5,6,11,13,15–18] The rise of metabolic intermediates such as kynurenine and quinolinic acid implicates the tryptophan-oxidation pathway and not other potential explanations for tryptophan loss in HIV-1 infection. Just as there are tissue differences in IDO production, so there is substantial variability in the capacity of different tissues to provide the necessary enzymes for the other major steps in the main oxidation pathway.[21]

Two critical steps exist in the main tryptophan oxidation pathway. First, the initial and rate-limiting step in tryptophan oxidation is activated by TDO or IDO and is the irreversible cleavage of the indole ring (figure 1). Once tryptophan is removed from the body's pool via oxidation it is no longer available for the other important uses, including its incorporation into proteins, and the minor oxidation pathway for the synthesis of serotonin and melatonin. In healthy adults, higher metabolic priority is given to tryptophan's incorporation into protein than to the conversion to niacin when the diet is experimentally manipulated.[22] There is some evidence that limited tryptophan in HIV-1-infected patients does not limit protein synthesis.[15] However, in HIV-1 infection, niacin is given metabolic priority over metabolic products such as serotonin (figure 2B).[6,23,24]

The second critical step is the conversion of aminocarboxymuconic semialdehyde to aminomuconic semialdehyde or quinolinic acid (figure 3). At this branch point, the fate of the carbon backbone is decided, taking the pathway towards niacin or that towards further oxidation. Picolinic carboxylase is the rate-limiting enzyme at this metabolic branch point. The oxidative conversion occurs preferentially, accounting for more than 90% of the end-product production. However, when picolinic carboxylase activity is limiting, a non-enzymatic reaction commits the molecule to the synthesis of niacin compounds.[1] In normal individuals, only 1–2% of total tryptophan intake is shunted down the non-enzymatic path to niacin. In HIV-1-infected people, circulating niacin concentrations increase proportionately to the decrease in circulating tryptophan (figure 2A and 2B).[25,26] The specific quantification of oxidative end products produced via increased aminomuconic semialdehyde pathway remains to be elucidated, but is also probably around 20% more than baseline.

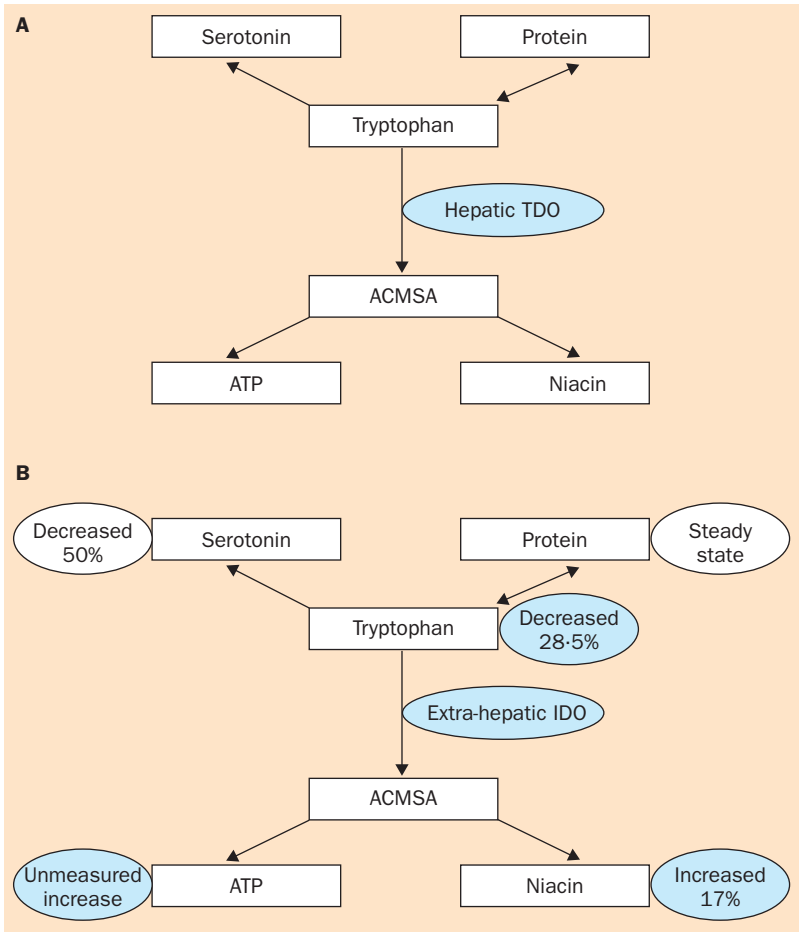

Figure 2. Basal metabolism of tryptophan in an uninfected person in nitrogen balance, and altered metabolism of tryptophan in an HIV-1-infected person. (A) Daily protein synthesis requires three and a half times as much tryptophan as the total dietary intake. This requirement is achieved by use of dietary tryptophan and tryptophan recycled from protein degradation. The minor oxidative pathway for tryptophan to form serotonin and melatonin accounts for around 1% of total dietary intake. Niacin production accounts for around 2% of total tryptophan intake, and occurs as a side reaction in the major oxidative pathway. Most of the remaining dietary tryptophan is either fully oxidised to create ATP, water, and carbon dioxide, or lost as urinary intermediates. Excess tryptophan is shunted down the major oxidative pathway via the hepatic enzyme TDO. (B) After infection protein turnover increases, but protein synthesis reaches a relative steady state as virus production reaches set point. Available tryptophan is shunted away from the minor oxidative metabolic pathway and out of the available pool into the inducible tryptophan oxidative pathway. This oxidation, at low concentrations, occurs extrahepatically via the enzyme IDO. Resting energy expenditure is increased in HIV-1-infected individuals, which necessitates increased ATP production, yet the amount of ATP via this pathway has not been measured. ACSMA=aminocarboxymuconic semialdehyde.

Tryptophan metabolism is disturbed throughout the course of HIV-1 infection (figure 2B), including the period before clinical symptoms. Despite a lack of overt signs or symptoms during early infection, several measurable changes occur, including raised interferon γ concentrations, a sustained rise in basal metabolic rate, a decrease in intracellular NAD, a chronic depletion of plasma tryptophan, and changes in the concentrations of related metabolites (eg, quinolinic acid and serotonin). Although

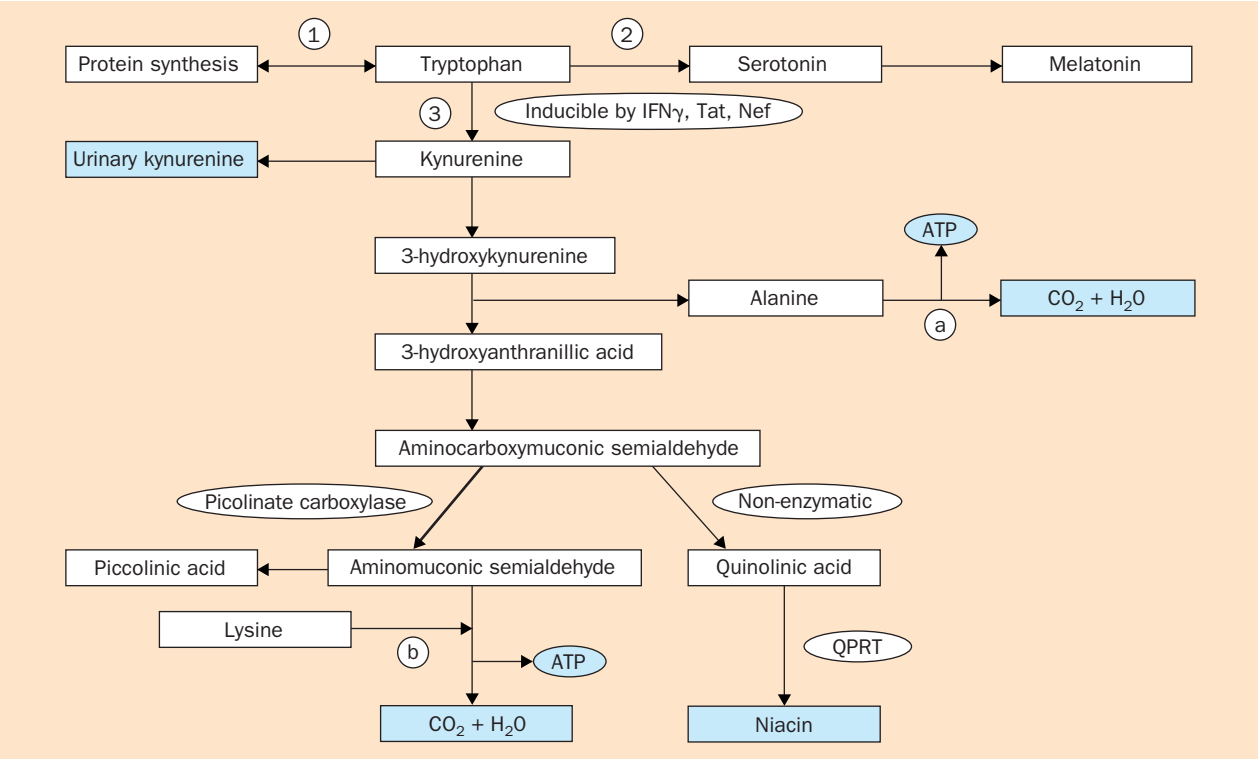

Figure 3. Availability of tryptophan. Available tryptophan can be used in one of three major pathways: (1) reversible incorporation into protein, (2) the minor oxidative pathway to serotonin and melatonin, and (3) oxidation for the production of energy and niacin compounds. Excess tryptophan induces the major oxidative pathway in the liver via TDO. Interferon γ, HIV-Tat, and HIV-Nef can all induce IDO to catalyse the initial rate-limiting step in tryptophan oxidation, irrespective of tryptophan concentrations at extrahepatic sites. The end products of oxidation are shown in blue. Tryptophan oxidation can increase glutamate (a) via increased alanine driving the conversion of αketoglutarate to glutamate. Lysine (b) and tryptophan partly share a common oxidative pathway, and excessive oxidation of either aminoacid may negatively feedback on the oxidation of the other. IFN=interferon. QPRT=quinolinate phosphoribosyl transferase.

further study is needed to fully understand the complex relations between tryptophan and HIV-1 infection, this review focuses on the potential links between disturbed tryptophan metabolism and pathogenesis.

Biological stimuli underlying inducible tryptophan oxidation

Cytokines

Cytokines stimulate IDO expression and activity. Although interferons α and β, tumour necrosis factor α, and platelet-activating factor can induce tryptophan oxidation, interferon γ seems to be the most important cytokine linked to this catabolism.[17,27–29] IDO induction can promote the removal of tryptophan in a localised microenvironment or systemically. Tryptophan oxidation driven by interferon γ can take place even when the circulating concentration of tryptophan is already low because of the relatively lower Km of IDO than that of TDO. Two concepts, applied separately, have been used to explain the removal of tryptophan via the host immune system: microbial aminoacid deprivation and immune tolerance. The fact that interferon γ induces a coordinated response within the cell that includes increased tryptophanyl-tRNA synthetase suggests that the cell prepares to meet the effects of the changes in tryptophan concentration on translation.[30] Interferon γ increases IDO expression to induce the rate-limiting step in tryptophan oxidation, but does not seem to affect other enzymes in the oxidative pathway such as kynurenine, 3-hydroxylase, and 3-OH-kynureninase.[31]

Non-viral infection

Non-viral intracellular pathogens, such as *Toxoplasma gondii* and *Chlamydia psittaci*, stimulate an interferon γ response and subsequent IDO-mediated tryptophan oxidation. In a mouse model of *T gondii* infection, the intraperitoneally injected protozoa localised to the lung and central nervous system (CNS) by 2 weeks, and detectable changes to the kynurenine: tryptophan ratio indicative of tryptophan oxidation were longest and most prominent in those organs.[32,33] These observations, together with in-vitro studies of *T gondii* and *Chlamydia* sp, have led to the hypotheses that host tryptophan modulation, in the microenvironment of the infection, results in a competitive advantage for the host.[34–36] The theory has been put forward that tryptophan depletion exists as a host strategy in these cases, aimed at decreasing microbial replication by starving intracellular parasites of tryptophan.[2] Such a host strategy in localised intracellular infections may confer a host advantage, but a systemic depletion of an essential aminoacid as a host immune strategy would seem unsustainable over long periods of time since the host also requires the aminoacid and cannot resynthesise it.

Table 1. Studies examining plasma or serum tryptophan in HIV-1-infected patients

Reference	Tryptophan concentration	Intervention	Other measures	Comments
Werner et al,[5] 1988	44·8 μmol/L in infected patients *vs* 91·0 μmol/L in controls	None specified	KT ratio 3/1 in patients *vs* controls	Increased KT ratio suggests increased tryptophan oxidation not dietary or other types of loss explain lower concentration
Larsson et al,[6] 1989	28·4 μmol/L in infected patients *vs* 39·7 μmol/L in controls	No patients on antiretroviral medications	Cerebrospinal fluid tryptophan 1·52 μmol/L in infected patients *vs* 2·18 μmol/L in controls	Lower tryptophan concentrations most pronounced at low CD4 counts
Fuchs et al,[7] 1990 (A)	48·8 μmol/L in infected patients with dementia or neuropathy, 70·5 μmol/L in patients without dementia or neuropathy, and 91·1 μmol/L in controls	None specified	Neopterin concentrations have a reciprocal relation to tryptophan concentrations	Neurological findings correlated with lower tryptophan concentrations
Fuchs et al,[8] 1990 (B)	29·8 μmol/L in infected patients *vs* 39·7 μmol/L in controls	None specified	Serum interferon γ concentrations 159 U/L in patient serum *vs* 33 U/L in control serum	Inverse correlation between tryptophan and interferon γ concentrations noted
Fuchs et al,[9] 1991	57 μmol/L in infected patients *vs* 91 μmol/L in controls	38% of patients on zidovudine monotherapy	Interferon γ 259 U/L in infected patients and 23·5 U/L in controls; kynurenine 3·45 μmol/L in infected patients *vs* 2·31μmol/L in controls	p<0·001 for inverse correlation between tryptophan and interferon γ concentrations. No separate analysis based on antiviral therapy
Wiegand et al,[10] 1991	45·0 μmol/L in patients with AIDS	28% on zidovudine monotherapy	Decreased plasma tryptophan associated with sleep disturbances	No separate analysis based on antiviral therapy
Heyes et al,[11] 1992	40·2 μmol/L in infected patients *vs* 70·9 μmol/L in controls	No patients on antivirals	Tryptophan decreases accompanied proportional increases in kynurenine and quinolinic acid in serum and cerebrospinal fluid	Raised concentrations of neurotoxic intermediate quinolinic acid demonstrated.
Gisslen et al,[12] 1994	29·4 μmol/L in infected patients pretreatment *vs* 36·2 μmol/L post-treatment	Zidovudine monotherapy for 3–14 months	No change in serotonin concentrations post-treatment·	Tryptophan increased 6·8 μmol/L (23%) post-treatment
Hortin et al,[13] 1994	22 μmol/L in infected patients *vs* 46 μmol/L in controls	85% of patients on mono or dual nucleoside therapy	Decreased cystine, tryptophan, methionine, increased taurine, lysine	Tryptophan and lysine showed trend of lower/higher with CD4 count <200/μL. No separate analysis based on antiviral treatment
Brown RR[3] 1996	Tryptophan concentration in infected patients lower than controls, and lower in AIDS than in asymptomatic infection	None specified	Correlation between lower tryptophan and failure to thrive·	Only paediatric patients studied
Eriksson et al,[14] 1996	Tryptophan concentration 50% lower in infected patients than in controls	None specified	No change in concentration of other large neutral aminoacids (ie, tyrosine, valine, phenylalanine, leucine, isoleucine)	Plasma ratios of tryptophan to other large neutral aminoacids predicted to affect active transport of tryptophan to CNS via shared transporter
Laurichesse et al,[15] 1998	51 μmol/L in infected patients *vs* 59 μmol/L in controls	None specified	Five other essential aminoacid concentrations also depressed (methionine, threonine, histidine, isoleucine, leucine)	Despite lower concentrations, tryptophan does not seem to be rate limiting in protein synthesis in AIDS patients
Huengsberg et al,[16] 1998	Tryptophan concentration 33·2 μmol/L in patients with AIDS, 50·1 μmol/L in people with asymptomatic HIV-1 infection, and 56·3 μmol/L in controls	None specified	Tryptophan concentration was 43·8 μmol/L in patients with CD4 less than 200, 44·0 μmol/L in patients with CD4 200–500, and 55·1 μmol/L in patients with CD4 greater than 500/μL	KT ratio and kynurenine concentrations had reciprocal relation to tryptophan. Advanced HIV disease correlates with evidence of increased tryptophan oxidation
Look et al,[17] 2000	44·6 μmol/L in infected patients pretreatment *vs* 53·0 μmol/L post-treatment	Individualised HAART regimens for 3 months	52·6 μmol/L in controls	Tryptophan increased 8·4 μmol/L (19%) post-treatment
Murray et al,[4] 2001	49·3 μmol/L in infected patients pretreatment *vs* 69·2 μmol/L post-treatment	Oral nicotinamide 3 g per day for 2 months. Patients were either on no antivirals or on a stable regimen for >2 years.	The concentration of cystine, methionine, taurine, and lysine remained unchanged by treatment. No separate analysis based on antiretroviral therapy	Tryptophan increased 19·9 μmol/L (40%) post-treatment
Zangerle et al,[18] 2002	44·1 μmol/L in infected patients pretreatment *vs* 53·2 μmol/L post-treatment	Individualised HAART regimens for 6 months	65·8 μmol/L in controls	Tryptophan increased 9·1 μmol/L (21%) post-treatment

Pregnancy

Pregnancy is associated with the stimulation of IDO. In mammals, survival of the fetus during pregnancy depends on tryptophan oxidation at the maternal-fetal interface.[37] Increased tryptophan oxidation during pregnancy was first recognised 50 years ago,[38,39] but its link to the immune response is a recent discovery.[40] Oxidation occurs at the placenta, but this localised phenomenon is the apparent driving force for systemic tryptophan depletion in pregnancy.[41,42] Pregnancy has long been known to induce a clinical state of relative immunodeficiency, particularly in cell-mediated responses,[43] and this deficient response is attributable, at least partly, to systemic tryptophan depletion. A change in immune reactivity is required for tolerance of the paternal antigens presented by the hemiallogenic fetus. In fact, the failure to suppress T-cell proliferative responses in pregnancy seems to be associated with recurrent miscarriage in human beings.[44] Since fetal cells and the paternal antigens they bear are present at the placental interface and in the maternal bloodstream (ie, fetal erythrocytes, lymphocytes, granulocytes, trophoblasts, and haemopoietic stem cells), systemic rather than simply localised immunotolerance is needed.[45] At the end of pregnancy the state of systemic immune tolerance driven by tryptophan oxidation resolves.

HIV-1 proteins

In HIV-1 infection tryptophan oxidation is stimulated by specific viral antigens. This observation raises the possibility that the virus benefits from activation of this metabolism. HIV-Nef and HIV-Tat, but not HIV-gp41 or HIV-gp120, induce IDO expression and tryptophan oxidation.[27] HIV-1 infection could have evolved mechanisms to initiate activation of this metabolic pathway to gain a competitive advantage over the host. In addition to effects in infected cells, HIV-Tat can be exported from infected cells and enter uninfected cells, so could potentially activate this pathway in a wide range of cell types.[46] Another viral antigen with potential relevance to viral activation of this metabolic pathway is HIV-p17, a matrix protein that localises to the nucleus and shares structural and functional features with interferon γ.[47] The specific question of whether HIV-p17's shared functions extend to IDO activation has not been examined. The interactions of other primate retroviruses with tryptophan metabolism are less well defined. However, there are changes in tryptophan concentration in human T cell lymphotrophic virus 1 (HTLV-1) infection,[48] and increases in tryptophan oxidation metabolites in simian immunodeficiency virus infection.[49]

Biological consequences of tryptophan catabolism by IDO

T-cell hyporesponsiveness

T-cell response to foreign antigens is depressed in the peripheral blood of HIV-1-infected individuals and pregnant women.[44,50] Increased IDO activity in HIV-1 infection results in decreased tryptophan and increased niacin, in a pattern reminiscent of human pregnancy (table 2).[25,26,42,53,54] This pattern of tryptophan-to-niacin metabolism in pregnancy is critical to conferring immune tolerance of foreign paternal antigens.[40] Cytokine-induced tryptophan oxidation has also been linked to the induction of tolerance of foreign antigens in other settings.[55] Further study is required to find out whether this metabolic pattern is linked to tolerance of HIV antigens. This potential link is, however, supported by the observation that HIV-1-associated T-cell anergy can be induced by HIV-Tat, the same viral protein that induces IDO expression and tryptophan oxidation.[50]

Changes in T-cell proliferation and viability

Tryptophan deprivation of T cells has also been linked to cell cycle arrest in G1 and cell death (table 2); these tryptophan-oxidation-associated phenomena could potentially contribute to the steady loss of circulating CD4 T lymphocytes, which is the hallmark of advancing disease in HIV-1 infection.[56] In-vitro studies show that T-cell G1 arrest can be reversed only with tryptophan repletion and restimulation of the T cell receptor, an observation with potential implications for structured treatment interruptions in patients.[56]

Table 2. Potential links between observed changes in HIV-1-infected patients and overactivation of inducible tryptophan oxidation

Reference	Observed change	Mechanism associated with tryptophan oxidation	Potential pathogenic effect
Heyes et al,[11] 1992	Raised quinolinic acid	Quinolinic acid is a metabolic intermediate of niacin coenzyme synthesis	Neurotoxic effects
Mellor and Munn,[40] 2001	T-cell depletion	T-cell proliferation defect associated with low extracellular tryptophan concentrations	Cell-cycle arrest in G1 and AICD
Mellor and Munn,[40] 2001	T-cell hyporesponsiveness	Defect in responsiveness to foreign antigen associated with low extracellular tryptophan concentrations	Immunotolerance
Launay et al,[23] 1989; Wiegand et al,[10] 1991	Decreased serotonin	Metabolic diversion from tryptophan's hydroxylative to oxidative pathway	Mood and sleep disorders
Grunfeld and Feingold,[51] 1992	Hypermetabolism/raised resting energy expenditure	Primary end products of tryptophan oxidation ATP, carbon dioxide, and water	Wasting
Ferrarese et al,[52] 2001	Increased glutamate	Tryptophan oxidation produces alanine, which converts a ketoglutarate to glutamate	Neurotoxic effects

AICD=activation-induced cell death.

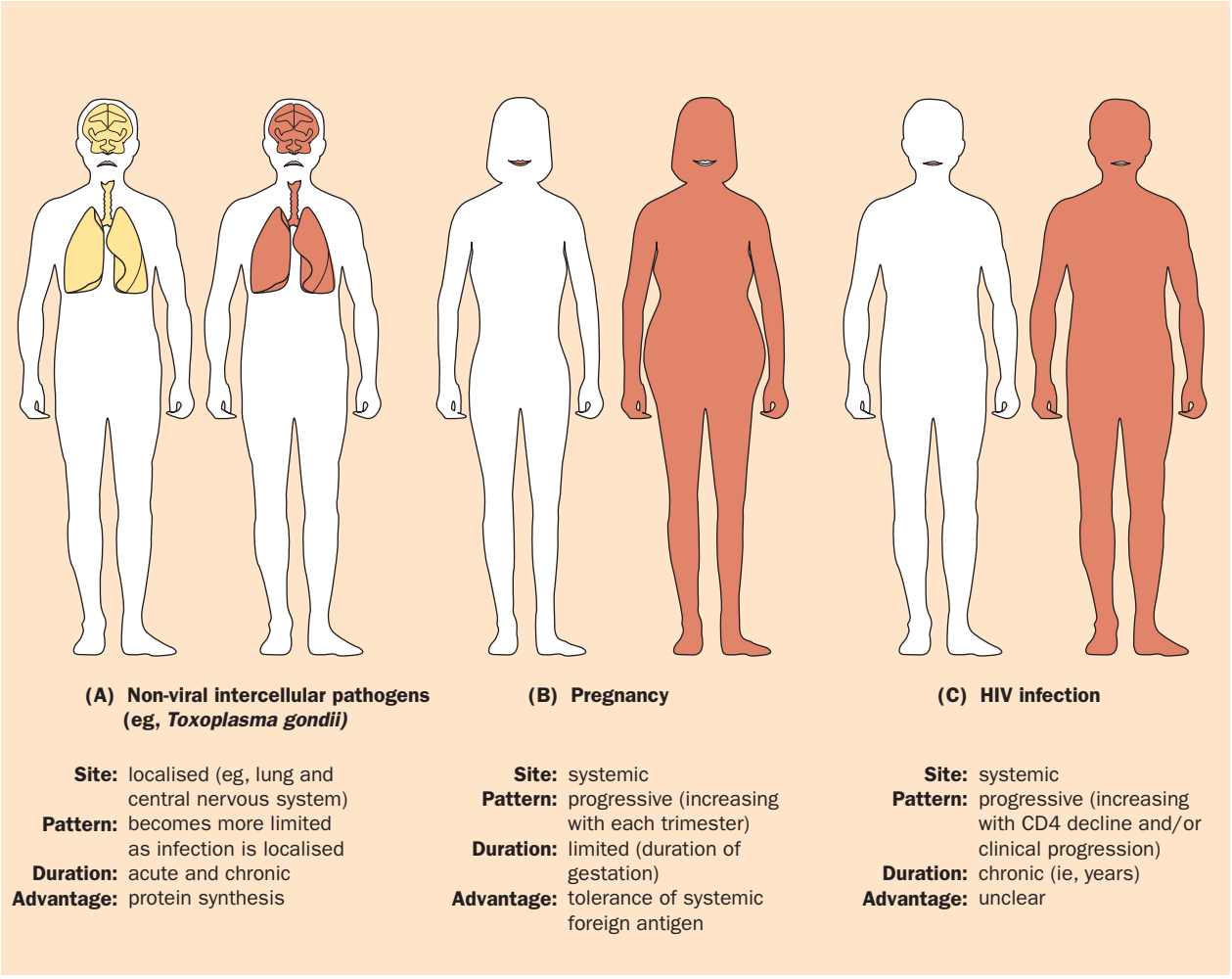

Figure 4. Model for three different immune modulating increases in extra-hepatic tryptophan oxidation. The host advantage conferred by localised tryptophan depletion in the microenvironment of (A) intercellular pathogens is believed to be based in the withholding of essential nutrients, and in (B) pregnancy it is believed to be survival of offspring. However, the prolonged systemic activation of this metabolism in (C) HIV infection does not confer any clear host advantage and may in fact confer advantage to the virus.

Quinolinic-acid production

Quinolinic acid is a neurotoxic metabolic intermediate of tryptophan oxidation along the niacin subpath (figure 3). Localisation of IDO activity and increased quinolinic acid in the brain has been associated with HIV dementia (table 2).[57,58] While the concentration of quinolinic acid is raised in the periphery and the CNS of HIV-1-infected individuals, the increase is proportionately higher in the CNS.[59] Although IDO activity initiates the metabolism, there may be a tissue-specific decrease in picolinic carboxylase or quinolinate phosphoribosyl transferase activity in the CNS to account for the increased concentrations there (figure 3). Quinolinic acid's neurotoxic effects are believed to be mediated by its excitotoxic activation of N-methyl-D-aspartate (NMDA) receptors. The specific quinolinic-acid inhibitors have been discussed,[58] but antiretrovirals that reduce extrahepatic tryptophan oxidation have proven effective in reducing quinolinic-acid concentrations clinically, thereby lowering the risk of dementia.[59]

Increased endogenous niacin

Increased tryptophan oxidation leads to a net increase in circulating niacin (table 2).[26] Such an increase has been documented in pregnancy and two infections associated with interferon γ—HIV and tuberculosis caused by *Mycobacterium tuberculosis*. Circulating niacin in these circumstances could have at least two potential effects. First, niacin might feedback to inhibit excessive tryptophan oxidation by IDO in the same way as niacin can inhibit TDO. Second, the availability of increased nicotinamide, the major circulating form of niacin, provides a precursor to cells for intercellular NAD production. In HIV-1 infection, intercellular NAD is decreased, putting infected and uninfected cells at risk of NAD-depleted cell death. Although NAD replenishment associated with tryptophan oxidation may be a host metabolic goal, this production of niacin via tryptophan oxidation comes at a significant energy cost, since the human body is inefficient at converting tryptophan to niacin.[60]

Altered metabolic rate

The increase in the basal metabolic rate of HIV-1-infected people remains poorly explained.[61,62] Resting energy expenditure is raised in all HIV-1-infected individuals, even if asymptomatic and with normal CD4 counts (table 2). Despite this increased resting energy expenditure, asymptomatic patients compensate and maintain normal bodyweights. A cytokine-driven mechanism, such as by tumour necrosis factor α, for increased resting energy expenditure has been suggested, yet studies have shown no correlation in HIV-1-infected people. Interferon γ as a stimulus for increased resting energy expenditure in HIV-1 infection has not been investigated. The tryptophan oxidation that HIV-Tat, HIV-Nef, and interferon γ drive results in energy production from a typically unavailable source—ie, in an individual in nitrogen balance tryptophan is not an energy source unless it is in excess. Therefore, extrahepatic tryptophan oxidation in HIV-1-infected people is a reasonable pathway to consider as a source for increased resting energy expenditure. Energy generated by tryptophan oxidation, especially the portion driven by viral antigens, wastes energy by uncoupling energy demands and energy production.[51] In support of the notion connecting tryptophan oxidation to resting energy expenditure, de Metz and colleagues[63] showed in normal volunteers that a dose of interferon γ sufficient to raise the circulating concentrations by 15–20-fold increases the resting energy expenditure by 11%. The expected increased ATP and carbon dioxide from extrahepatic tryptophan oxidation can explain at least part of the resting energy expenditure phenomenon in HIV-1 infection. The exact contribution of this metabolism to the increased resting energy expenditure in HIV-1-positive patients remains to be quantified.[25]

Changes in associated metabolites

In HIV-1-infected individuals, alterations to other molecules whose metabolism is linked to tryptophan oxidation might have additional consequences (table 2). The potential pathogenic links between decreased tryptophan and these molecules (ie, serotonin, melatonin, glutamine, lysine, and picolinic acid) need to be further assessed. The hydroxylative metabolism of tryptophan produces serotonin and melatonin. The concentration of serotonin in the brain depends on plasma tryptophan concentrations,[64] and several studies show clearly that serotonin in the CNS and the periphery is diminished. Although melatonin concentrations have not been studied directly, these are likely to be proportionately decreased since it is synthesised from serotonin. Decreased serotonin and melatonin could potentially result in mood and sleep disturbances. Two aminoacids whose concentrations are increased in HIV-1-infected individuals and whose metabolism is linked to tryptophan oxidation are glutamate[52] and lysine (figure 3).[13,65] Lastly, picolinic acid, which is a side product of tryptophan oxidation (figure 3), can inhibit T-lymphocyte proliferation,[66] and inhibit HIV-1 replication.[67] Measurement of picolinic-acid concentrations in HIV have not been reported.

Search strategy and selection criteria

Data for this review were identified by searches of Medline, the science citation index, and references from relevant articles. Search terms were "HIV", "AIDS", "tryptophan", "immune function", "T-cell function", "metabolism", "nutrition", and "pregnancy". References were not limited by language or year of publication.

Conclusion

The net advantage of tryptophan oxidation in HIV-1 infection is unclear. Host immune-mediated activation of this metabolism might have as its goal the removal of tryptophan from the available aminoacid pool, the production of the pathway's metabolic end products, the production of the pathway's metabolic intermediates, or some combination of these. This general phenomenon is also seen with other infections, malignant disease, and autoimmunity. The metabolic activation could be harmful to the host by slowing T-cell responses. It is also possible that in the context of HIV-1 infection that there is an inadvertent host activation (or overactivation) of this pathway on the way to achieving another goal mediated by interferon γ such as nitric oxide synthetase activation.[68] Another novel possibility that deserves attention is that substantial benefit from tryptophan oxidation in HIV-1-infected people goes to the virus, which, in vitro, induces this metabolism over and above any endogenous cytokine activation via its own antigens (ie, HIV-Tat and HIV-Nef). Although such a finding has not been validated in vivo, Chiarugi and colleagues' finding[69] that decreased tryptophan can selectively block increases in inducible nitric oxide synthase mediated by interferon γ provides an example of a potential viral advantage to increased tryptophan oxidation.

A model can be suggested contrasting three different settings for increased extrahepatic tryptophan oxidation responses (figure 4). These settings are: non-viral intracellular pathogens, pregnancy, and HIV-1 infection. The localised and coordinated induction of tryptophan oxidation by the immune system seems to be a host strategy aimed at achieving a competitive advantage over intracellular microbes such as *T gondii* and *Chlamydia* sp. In pregnancy, there is a systemic depletion of tryptophan associated with localised induction of tryptophan oxidation at the maternal-fetal interface that seems to be an immunotolerant strategy aimed at accommodating the foreign fetal antigens presented systemically and locally. In HIV-1 infection there is an open-ended, progressive, systemic induction of tryptophan oxidation that is driven partly by viral proteins; this specific induction of tryptophan oxidation by viral antigens may be a critical pathogenic step that overactivates a normal host-immune strategy.

Two different interventions can increase tryptophan concentrations in HIV-1-infected individuals: antiviral treatment and niacin treatment. The host benefits of antiretroviral treatment are well documented. Further study of niacin supplementation will be required before any conclusions about its role in HIV-1-infection can be stated. Niacin supplementation is also, however, clinically beneficial to HIV-1-infected individuals; specifically, it has been associated with increased CD4 counts, slowed progression to AIDS, and prolonged survival.[70–72] Niacin, in the form of

nicotinamide, reverses tryptophan depletion, and this action may be central to the observed benefits. Antiretrovirals and niacin inhibit tryptophan oxidation in vivo. By contrast, any strategy that seeks to replete tryptophan in HIV-1-infected people by direct dietary supplementation of the aminoacid may inadvertently fuel tryptophan oxidation, raise quinolinic-acid production, and thereby exacerbate the neurotoxic effects of tryptophan oxidation. Therapeutic strategies aimed at regulating tryptophan oxidation may prove useful for patients infected with HIV-1, particularly those who have limited dietary protein and whose routine tryptophan intake is less than that provided by the typical diet in developed countries.

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Conflicts of interest

I have no conflicts of interest to declare in relation to this review.

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