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REVIEW

Immune activation and neuropsychiatric symptoms in human immunodeficiency virus type 1 infection

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Abstract: Human immunodeficiency virus type 1 (HIV-1) infection is associated with a wide range of neuropsychiatric symptoms, especially in the later course of the disease. In addition to a direct effect of HIV-1 causing irreversible loss of brain cells, neurological impairment may relate to metabolic factors. Immune activation and the inflammatory response involving immunocompetent cells seem to play a major role. Existing data suggest that immune activation and inflammatory responses can cause metabolic disturbances, which can be reversible to some extent, eg, when highly active antiretroviral therapy is successful. Immune-related tryptophan catabolism and impaired phenylalanine hydroxylase (PAH) activity have been described in HIV-1 infected patients. These enzyme systems are deeply involved in the biosynthesis of important neurotransmitters and biogenic amines like 5-hydroxytryptamin (serotonin) from tryptophan, and dopamine, adrenaline, and noradrenaline from phenylalanine. Thus, any disturbance of their biosynthesis may contribute to neurological and psychiatric symptoms, such as depression, cognitive impairment, and memory loss. In addition to highly active antiretroviral therapy, popular antidepressant medication with selective serotonin reuptake inhibitors or also noradrenaline and dopamine reuptake inhibitors will be of help to improve neuropsychiatric abnormalities in patients with HIV-1 infection. It will be interesting to know whether measurements of tryptophan degradation and of PAH activity might be able to guide treatment with antidepressants and thereby improve treatment efficacy in HIV-1 infected patients suffering from cognitive impairment, mood changes, and depression.

Keywords: HIV-1, tryptophan, neopterin, indoleamine 2,3-dioxygenase, phenylalanine

Introduction

Patients with human immunodeficiency virus type 1 (HIV-1) infection show a progressive loss of immune function, which is due to the decline of $CD4^+$ T helper cells in numbers and function, both of which together are responsible for the increased risk of opportunistic infections in patients in the absence of adequate antiretroviral therapy.[1] However, this state of immunodeficiency is associated with strong and overwhelming immune system activation, which primarily involves T cells and macrophages (Figure 1).[1–3] Along with multiple other signs of chronic immune activation, increased concentrations of neopterin (D-erythro 1′,2′,3′-trihydroxypropylpterin) were described in the body fluids of patients with HIV-1 infection as far back as the late 1980s.[2–7] Neopterin concentrations in serum, plasma, and urine of patients with HIV-1 infection correlate with HIV-1 load and the loss of $CD4^+$ cells throughout the disease course, and are of equal or even superior prognostic value for the future course of disease in patients compared with $CD4^+$ counts or even HIV load, and this is even true after

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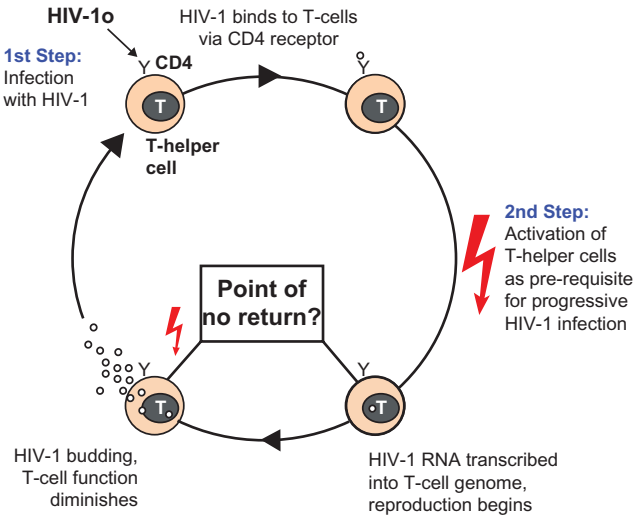

Figure 1 Immune activation and HIV-1 infection. Immune activation plays a crucial role in the pathogenesis of HIV-1 infection and acquired immune deficiency. Activated T cells are more susceptible to infection with HIV-1, and the activation of infected T cells induces HIV-1 replication (indicated by flash symbols). Immune activation is induced by HIV-1 infection itself, and also by secondary infection with other viruses or intracellular pathogens like *Mycobacterium tuberculosis*. The central role of immune activation is reflected by increased neopterin concentrations in patients infected with HIV-1. They reflect activated T cells and macrophages, correlate closely with the clinical course, and are strongly predictive of the future course of the disease.
Figure adapted from Fuchs et al.[2,3] This figure was published in Cancer detection and prevention, volume 1, Fuchs et al, Activated T-cells in addition to LAV/HTLV-III infection: A necessary precondition for development of AIDS, pp. 583–587, Copyright Elsevier (1987).
Abbreviation: HIV-1, human immunodeficiency virus type 1.

the introduction of highly active antiretroviral therapy (HAART).[8] On successful antiretroviral therapy and HAART, concentrations of neopterin and other immune activation markers like 75 kDa soluble tumor necrosis factor receptors (sTNF-R75) decline in parallel with HIV-1 load and mirror the increase in $CD4^+$ count.[9]

Patients suffering from progressive HIV-1 infection often experience impaired quality of life. In parallel, they also tend to have neurological/psychiatric disorders more often.[10–12] Interestingly, elevated neopterin levels have also been observed in HIV-1-negative patients with depression, and a link between immune activation and development of depression has been suggested.[13–15] In patients with HIV-1 infection, signs of immune activation were found to relate to neuropsychiatric disturbances.[16] Higher neopterin concentrations in cerebrospinal fluid (CSF) were found in HIV-infected patients with neurological/psychiatric symptoms in comparison with patients without neurological/psychiatric symptoms.[17] In addition to other parameters, like immune-mediated catabolism of the essential amino acid tryptophan, which may impair the synthesis of abnormal neurotransmitters like 5-hydroxytryptamine (serotonin), dopamine and/or noradrenaline metabolism might influence quality of life in HIV-patients.

Biochemistry of neurotransmitters and cofactors

In the early 1980s it was discovered that increased amounts of neopterin are formed and released by human monocyte-derived macrophages preferentially upon induction with Th1-type cytokine interferon (IFN)-γ.[18] Later on, it was found that human dendritic cells and astrocytes can also induce significant neopterin production via proinflammatory stimuli.[19,20] Analogously, increased neopterin concentrations detected in the blood of patients could be referred to an activated cellular (Th1-type) immune response.[21] Therefore, it is important to realize that only primate, either human or nonhuman, monocytic cells are capable of producing neopterin at high output rates, whereas other human cells or cells from other species do not (Figure 2). Neopterin derives from guanosine triphosphate (GTP), which is cleaved by the IFN-γ-inducible enzyme, GTP cyclohydrolase I (EC 3.5.4.16),[22] to the intermediate product, 7,8-dihydroneopterin triphosphate. This unstable compound is the precursor molecule for the production of 5,6,7,8-tetrahydrobiopterin (BH4), the well established cofactor of the mono-oxygenases PAH (EC 1.14.13.39), tyrosine 5-hydroxylase (EC 1.14.16.2), tryptophan 5-hydroxylase (EC 1.14.16.4), and nitric oxide synthases (EC 1.14.13.39)[23,24] and, more recently shown, of glycerylether monoxygenase.[25] Human monocyte-derived macrophages produce neopterin at the expense of biopterin

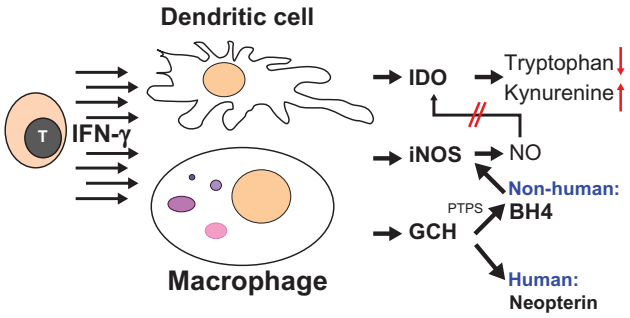

Figure 2 Antiproliferative effector mechanisms within the Th1-type immune response. Among other cytokines, activated Th1-type lymphocytes release large amounts of the proinflammatory cytokine IFN-γ, which is an important forward regulator of the Th1-type immune response and also a strong trigger of antimicrobial and antitumoral enzyme pathways. These include the tryptophan-degrading enzyme, IDO, NO formation by iNOS, and the formation of BH4 and neopterin by GCH. These metabolic pathways are intertwined, ie, BH4 is required as a cofactor of iNOS and is produced by a secondary enzyme known as 6-pyruvoyl-tetrahydropterinsynthase, a deficiency of which in human monocyte-derived dendritic cells and macrophages leads to accumulation of neopterin at the expense of BH4. Therefore, BH4 output by iNOS is low in these cells in humans but not in other species. Activated iNOS in human cells produces a superoxide anion instead of NO. In species other than humans, NO interferes with IDO expression and function, thus diminishing IDO activity.
Abbreviations: IDO, indoleamine 2,3-dioxygenase; NO, nitric oxide; iNOS, inducible nitric oxide synthase; BH4, 5,6,7,8-tetrahydrobiopterin; IFN-γ, interferon gamma; GCH, GTP-cyclohydrolase I.

derivatives due to an only low activity of pyruvoyl tetrahydropterin synthase (EC 4.2.3.12), the second enzyme required for BH4 biosynthesis.[22] Accordingly, human macrophages suffer from a malfunctioning of cytokine-inducible nitric oxide synthase (iNOS, Figure 2).[26] However, any other cell type capable of responding to proinflammatory stimuli like IFN-γ upregulates its production rate of BH4 during states of immune activation and inflammation (Figure 2).

Neurological and psychiatric impairment in HIV-1 infection

Neurological and psychiatric impairment often develops in patients with acquired immune deficiency syndrome (AIDS). It is related to opportunistic infections and direct neuronal infection by HIV-1 leading to HIV-1 encephalitis. The HIV-1-associated dementia and the AIDS dementia complex were recognized early in the AIDS epidemic,[27,28] because HIV-1 invades the central nervous system early in the course of infection and establishes a protected viral reservoir. However, neurocognitive impairment develops only in a small portion of infected patients.[29] Irreversible loss of brain tissue in patients with HIV-1 infection is supposed to be due to direct cytopathic effects of HIV-1 on neuronal and glial cells, which still awaits unequivocal demonstration.

Risk of neurocognitive impairment in patients with HIV-1 infection correlates with the nadir of $CD4^+$ cell counts, and increases when CSF viral load becomes equal to or higher than plasma viral load.[30] Overall cerebral volume, including gray and white matter volume and volumes of the parietal, temporal, and frontal lobes and the hippocampus, are most strongly associated with disease history factors like nadir $CD4^+$ counts and duration of infection. Such findings indicate that individuals with a history of chronic HIV infection with severely impaired immune function may be at greatest risk for cerebral atrophy.[31] Other risk factors include vascular disease and reduced resting cerebral blood flow, as well as genetic factors of the host and of HIV-1. Interestingly, the nadir $CD4^+$ count was also found to be associated with the extent of the initial immune response cascade, because serum levels of soluble immune activation marker, β2-microglobulin, and neopterin increase significantly during the acute infection episode, at least 6 months before the $CD4^+$ counts decline.[32] In contrast, increases in mean HIV RNA levels occur at the time of the $CD4^+$ cell decline. These data are consistent with the view that in vivo immune activation precedes the increases in HIV-1 load and is followed by an accelerated and rapid loss of $CD4^+$ lymphocytes.

Activated immunocompetent cells in the brain like microglia or invaded macrophages could indirectly mediate the neurological damage, eg, by the synthesis of neurotoxic factors. In addition to cognitive impairment, depressive mood is also a frequent symptom in patients with progressed HIV-1 infection,[33,34] and, as is known from other clinical conditions, impaired serotonergic and/or dopaminergic neurotransmission may play a role in the precipitation of depressive symptoms in patients.[14,15,35–40]

Accelerated degradation of the essential amino acid, tryptophan, can be caused by increased expression of indoleamine 2,3-dioxygenase (IDO, EC 1.13.11.52), an enzyme expressed during states of inflammation and immune activation.[14,15,36,37] The decline of tryptophan concentrations may impair serotonin formation that is crucial for neuropsychiatric performance.[14] Likewise, many HIV-1 infected patients with depression respond well to treatment with selective serotonin reuptake inhibitors, but others do not.[41] This observation suggests that other factors could also be crucial, ie, specific HIV-1 proteins could exert a neurotoxic effect[42] and neurotoxic activities of some tryptophan catabolites, like quinolinic acid, could play a role.[37,43,44] Additionally, altered metabolism of catecholamines, ie, dopamine, adrenaline (epinephrine), and noradrenaline (norepinephrine), might also be important (Figure 3).[39,45]

Increased degradation of tryptophan by IDO induced by immune activation

Like neopterin production, IDO is activated by proinflammatory stimuli, the most important one being IFN-γ.[36,46] However, unlike neopterin synthesis, tryptophan degradation via the kynurenine-pathway by IDO is not only stimulated in human monocyte-derived macrophages and dendritic cells, but also inducible in various other cells, like endothelial cells, epithelial cells, and fibroblasts, and also in species other than humans and primates.[47] Kynurenine is the first detectable product within the degradation pathway and so the kynurenine to tryptophan ratio (Kyn/Trp) serves as a good estimate of the extent of tryptophan degradation.[17,36,48] However, it has to be kept in mind that IDO is not the only tryptophan-degrading enzyme, and that hepatic tryptophan 2,3-dioxygenase (TDO, EC 1.13.11.11) can also be of relevance. Still, IDO is cytokine-inducible, whereas the isoenzyme TDO is regulated by tryptophan availability and upregulated by steroid hormones.[43] Direct measurement of IDO activity would require analysis at the cellular level, which is usually not readily available. However, when

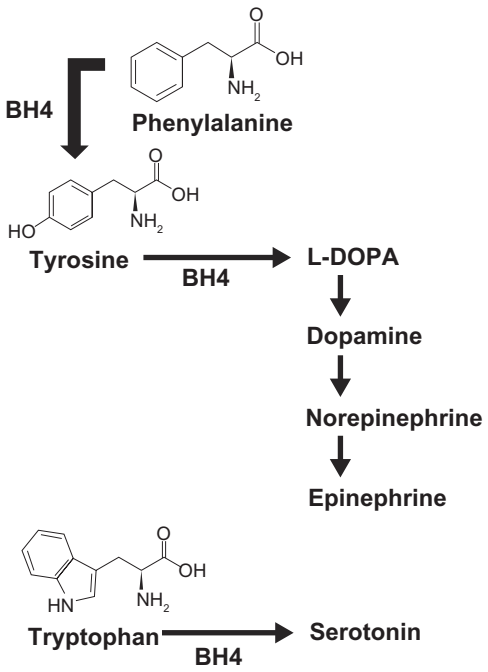

Figure 3 Role of BH4 in the biosynthesis of neurotransmitters from aromatic amino acids. BH4 is a cofactor of phenylalanine 4-hydroxylase, converting phenylalanine to tyrosine. Subsequent conversion of tyrosine to L-dopa by tyrosine 3-hydroxylase also requires BH4 as cofactor, with L-dopa serving as a substrate for the production of neurotransmitters, ie, dopamine, norepinephrine (noradrenaline), and epinephrine (adrenaline). BH4 is also a cofactor for tryptophan 5-hydroxylase, converting tryptophan to 5-hydroxytryptophan, which is decarboxylated to form the neurotransmitter serotonin (5-hydroxytryptamine).
Abbreviation: BH4, 5,6,7,8-tetrahydrobiopterin.

an activated immune system is detected by, eg, increased concentrations of neopterin, sTNF-R75,[9] or similar representative markers, and a correlation exists between Kyn/Trp and concentrations of one of these markers, the probability that enhanced Kyn/Trp is due to activated IDO becomes very high.[17,36] In HIV-1 infection, significant associations were demonstrated to exist not only between tryptophan metabolism and neopterin levels, but also with circulating IFN-γ concentrations.[48] However, no extrapolation solely from Kyn/Trp to any cellular source is possible, but when a concurrent increase in neopterin levels is measured, at least a contribution of monocytes/macrophages or dendritic cells is suggested.

Accelerated immune-mediated degradation of tryptophan by IDO may contribute to a deficiency of serotonin, the biosynthesis of which involves tryptophan as a precursor molecule (Figure 2). This relationship could be of particular importance in the pathogenesis of memory loss and depression in patients with HIV-1 infection.[49] Lowered serotonin concentrations have been described in the blood and CSF of patients with HIV-1 infection.[50,51] However, not only tryptophan deficiency may cause serotonin deficiency due to its accelerated degradation; serotonin, as an indoleamine derivative, is accepted as a substrate by IDO, albeit with lower affinity than tryptophan.[36]

In addition to serotonin deficiency, the formation of specific products within the tryptophan degradation pathway can also play a role in the development of neuropsychiatric disturbances in patients with HIV-1 infection. Quinolinic acid is an important downstream catabolic product of tryptophan,[43] and accumulation of quinolinic acid in patients suffering from inflammatory conditions[52] can also be interpreted as a sign of activated IDO. However, with the same limitations as Kyn/Trp measurements, in the case of elevated quinolinic acid, TDO cannot be ruled out as a player in the background, and only in the presence of an inflammatory response it becomes more likely that elevated concentrations indicate IDO involvement. Additional enzymes like kynurenine mono-oxygenase, kynureninase, and 3-hydroxyanthranilate dioxygenase need to be functionally active for synthesis of quinolinic acid, and an adequate supply of pyridoxal phosphate (vitamin B6) is required for proper function of the enzyme network.[43] As with neopterin synthesis, macrophages and dendritic cells possess this enzymatic repertoire and are thus major sources of quinolinic acid production aside from liver cells.[44,47,53]

Given that the biochemistry around nitric oxide formation is intertwined with the metabolism of neopterin and BH4,[26] it also interferes with tryptophan metabolism, because nitric oxide inhibits IDO activity in interferon-γ-primed mononuclear phagocytes (Figure 2).[54] Because iNOS activity is almost completely absent in human monocytes/macrophages, it is much easier to detect IDO activity in humans without gross interference by nitric oxide. Moreover, the high output nitric oxide formation by iNOS in nonhuman macrophages can also interfere with the measurement of kynurenine in, eg, rat and mouse serum, plasma, and tissue, when kynurenine is destroyed by diazotization upon acidification for protein precipitation prior to high-pressure liquid chromatography.[55]

Regarding IDO, a special situation might exist in the course of HIV-1 infection, given that the immunomodulatory effects of specific HIV-1 proteins are not only well established, but a direct effect of transactivator protein HIV-1-Tat to induce brain cytokines and IDO was also demonstrated recently.[56,57]

Decreased activity of PAH in immune activation disorders

Symptoms like anhedonia and clinical signs of depression can develop in patients related to disturbed dopamine metabolism,[58] eg, due to impaired enzymatic conversion

of phenylalanine.[39,45] Decades ago, increased blood concentrations of phenylalanine were described in patients with various clinical conditions, along with signs of immune activation and inflammation, including HIV-1 infection.[59] The reason for this abnormality is still unexplained, but most likely an impaired function of the PAH enzyme underlies the phenylalanine accumulation (Figure 3).[39]

Phenylalanine is the precursor of tyrosine, another proteinogenic amino acid, which is an important precursor for the biosynthesis of L-dopa(L-3,4-dihydroxyphenylalanine) and for dopamine, adrenaline, and noradrenaline (Figure 2).[39] For enzymatic hydroxylation of phenylalanine to tyrosine by PAH, the cofactor BH4, ie, the reduced form of biopterin, is required as a hydrogen donor.[23] PAH is extremely sensitive to oxidation,[60,61] and if BH4 is destroyed, the conversion rate of phenylalanine to tyrosine by PAH is reflected in an increased ratio of phenylalanine to tyrosine concentrations (Phe/Tyr), which is a useful measure of PAH activity, and better than phenylalanine alone.[62,63] Likewise, Phe/Tyr can also be regarded as a surrogate of the functional activity of BH4.

Oxidative stress due to chronic immune activation and inflammation could be involved in the increase in serum phenylalanine concentrations in patients. Recently, we described a correlation between Phe/Tyr and neopterin concentrations in patients after multiple trauma, with ovarian cancer, or with HIV-1 infection.[64–66] Moreover, HAART in patients with HIV-1 infection was not only associated with increased $CD4^+$ cell counts and reduced HIV-1 load and neopterin concentrations, but also with decreased Phe/Tyr and phenylalanine concentrations,[66] indicating that immune activation is related to impaired PAH functional activity. This conclusion is further substantiated by recent findings that IFN-γ treatment in patients with hepatitis C virus infection led to a significant increase of phenylalanine levels and Phe/Tyr.[67] The mechanism underlying PAH impairment might involve oxidative stress due to the high output of reactive oxygen species by, eg, activated monocytes/macrophages which may destroy BH4 and/or influence substrate and/or cofactor binding when changes in the tertiary structure of PAH are caused by oxidation of, eg, sulfhydryl groups.[68]

Aside from the disturbed fundamental biochemistry of phenylalanine, neurotoxic products accumulating upon IDO activation can also contribute to dopaminergic alterations, eg, quinolinic acid has been demonstrated to alter the mesolimbic dopaminergic system directly and to induce dopaminergic neuronal death, while kynurenic acid, a tryptophan metabolite, controls the firing of dopaminergic neurons in the midbrain.[69]

Immune activation-induced metabolic changes and neuropsychiatric symptoms in HIV-1

Higher neopterin concentrations have been described in patients who suffer from neuropsychiatric complications[70] in addition to HIV-1,[71] compared with those without such complications. This is especially true in the CSF, although neopterin concentrations in serum or plasma are also significantly associated with CSF levels. Neopterin concentrations in the CSF of patients with AIDS dementia complex correlate with the severity of dementia and decreased along with clinical improvement following treatment with zidovudine therapy.[72] Interestingly, neopterin concentrations in serum have been found to correlate significantly with brain tissue loss, as reflected by the ventricle brain ratio, according to computed tomography results.[16] Similar observations were made when brain tissue loss was compared with quinolinic acid concentrations in the CSF.[44] Higher serum neopterin concentrations also correlated inversely with the cognitive performance of patients as determined by scores on the Structured Interview for the Diagnosis of Alzheimer Dementia and dementia of other etiology.[16]

All these findings indicate that immune activation and immune activation-induced biochemical alterations are involved in the precipitation of neuropsychiatric symptoms in patients infected with HIV-1. However, immune activation and inflammatory responses may not only be involved in irreversible loss of brain tissue, but may also cause metabolic disturbances, the reversibility of which is more likely when, eg, HAART is successfully administered. Among the biochemical alterations induced by HIV-1, degradation of tryptophan by the IDO enzyme has received greater attention. Findings from in vitro and in vivo studies and from animal model systems support the concept that tryptophan degradation by IDO plays a major role in inflammation-associated neuropsychiatric disorders such as depression and cognitive decline.[14,15,36] Serum tryptophan concentrations were lower in HIV-1 infected patients with worse cognitive performance,[17,72] and lower tryptophan levels were also associated with sleep disturbances.[73]

Abnormal phenylalanine metabolism was also recently demonstrated to be quite common in patients with HIV-1 infection,[59,66] although fewer data on clinical correlates are presently available, as compared with studies on IDO. In patients outside the field of HIV-1 infection, eg, the elderly, several significant associations have been demonstrated between the increase in phenylalanine and Phe/Tyr in the blood and specific neuropsychiatric

symptoms.[74] Phenylalanine metabolism was mostly related to general behavioral and neurovegetative symptoms according to the neurotoxicity rating scale like sleep alterations, sickness, and digestive and motor symptoms, whereas changes in immune activation markers (neopterin) and tryptophan metabolism were more associated with depression scores according to the Montgomery-Asberg Depression Scale. Greater disturbances correlated with reduced appetite and pessimistic thoughts and also fatigue symptoms like reduced motivation. Conversely, general behavioral and neurovegetative symptoms like sleep alterations, sickness, digestive symptoms, and motor symptoms, correlated more closely with phenylalanine than tryptophan metabolic abnormalities.[74]

In patients with HIV-1 infection, depression and impaired quality of life are frequently observed, and in a relatively large study of 154 patients, Beck's Depression Inventory and quality of life scores were compared with prognostic parameters of HIV-1 infection, including neopterin and Kyn/Trp. Beck's Depression Inventory and quality of life were closely associated with each other, and patients with depression had significantly higher plasma neopterin concentrations, lower $CD4^+$ cell counts, and hemoglobin concentrations, as well as better quality of life scores than nondepressed patients, who also showed lower rates of tryptophan degradation. High neopterin concentrations and low hemoglobin levels were the best predictors of depression, whereas hemoglobin levels and viral load were predictive of impaired quality of life.[75] Unfortunately, no CSF specimens were available in that study.

In addition to the association between tryptophan degradation and mood changes in patients with HIV-1 infection, another study showed acute psychotic symptoms to be associated with increased levels of kynurenic acid in CSF, which were most probably due to enhanced IDO activity.[76] Notably, signs of immune activation are detectable in the brains of patients with HIV-1 infection even when viral burden in the CSF is minimal.[77]

Influence of HAART on immune activation and other therapeutic considerations

Antiretroviral therapy is well known to be able to improve the neuropsychiatric status of HIV-1-infected patients.[78] In parallel with the increase in $CD4^+$ counts and the decline of HIV-1 load under HAART, there is a decline in serum, plasma, and urinary neopterin concentrations, and of, eg, soluble TNF-R75.[79–82] A significant reduction of neopterin concentrations in CSF is achieved under HAART.[82,83] The same is true for the tryptophan degradation rate, in that Kyn/Trp is often highly elevated in patients with HIV-1 infection, and a significant drop of Kyn/Trp takes place, which is due to an increase in tryptophan and a decline in kynurenine concentrations.[80] Phenylalanine concentrations and Phe/Tyr also decline significantly on HAART,[66] and this decline correlates with changes in neopterin concentrations. However, so far, no studies are available in which marker changes are compared with neuropsychiatric performance of patients, except for one case report, in which concurrent improvement in neurological symptoms and normalization of CSF biomarkers were observed following HAART in a patient with HIV-1-associated dementia.[82] However, even on long-term therapy with HAART, chronically enhanced immune activation, albeit at a low level, can be observed in patients,[84] indicating viral escape into the CSF despite suppression of plasma HIV-1. Thus, low-grade central nervous system infection may continue in treated patients.[85]

Treatment concepts targeting IDO activity using the specific inhibitor, 1-methyl tryptophan, are the focus of intense research.[86] The rationale behind this therapeutic strategy is to revert the negative effects of IDO on T cell responsiveness, thereby improving the functional anti-HIV-1 immune response in patients.[87] Because activation of IDO is also part of the antiviral strategies in immunocompetent cells, inhibition of IDO would not only improve tryptophan availability to immunocompetent cells, but may also carry a risk of accelerating HIV-1 reproduction. On the other hand, inhibiting IDO would also increase tryptophan availability for serotonin biosynthesis and reduce the formation of neurotoxic catabolites. Both these effects could contribute to improvement in neuropsychiatric symptoms in patients (Figure 4). A similar scenario might take place when supplementation with tryptophan is considered. In this case both the proliferation and reproduction of HIV-1 might increase, and any benefit for the patient is unclear and cannot be predicted. Moreover, increasing the tryptophan pool would also increase the production of catabolites, some of which have neurotoxic potential.

Studies in in vitro culture systems of peripheral blood mononuclear cells and of monocytic cell lines like THP-1 cells show that anti-inflammatory compounds, such as aspirin and lipid-lowering 3-methylglutaryl-coenzyme-A (HMG-CoA) reductase inhibitors (statins), are able to slow down IDO activity and neopterin formation.[88,89] The same is true for various antioxidant compounds, including vitamin C and E, as well as the stilbene, resveratrol.[90,91] Corresponding data from in vivo studies are not available, but lower neopterin concentrations are observed in patients at risk for cardiovascular disease taking statins.[92]

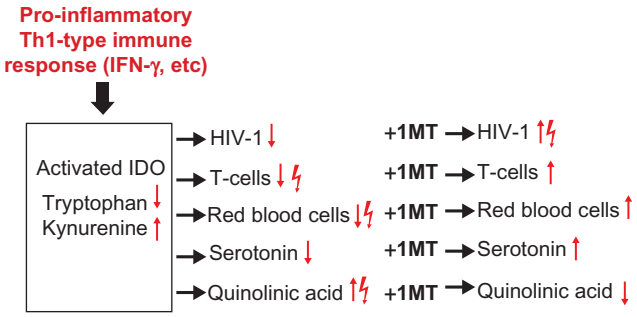

Figure 4 IDO during the proinflammatory immune response in HIV-1 infection. Consequences of increased IDO activity comprise a slowing down of HIV-1 reproduction (beneficial for the host) but also suppression of lymphopoiesis and hematopoiesis contributing to immunodeficiency and anemia. In addition, availability of serotonin is diminished when tryptophan concentrations become low upon degradation, and serotonin itself is also accepted as a substrate by IDO. In addition, downstream metabolites of kynurenine like neurotoxic quinolinic acid and other products (indicated by dots) accumulate. Inhibition of IDO by 1-methyl-tryptophan would improve immune and hematopoiesis status by increasing tryptophan availability, and neuropsychiatric status will benefit from increased serotonin production and decreased potential neurotoxins. However, HIV-1 reproduction would also benefit from increased availability of tryptophan. Therefore, this therapeutic strategy can provide overall benefit only when HIV-1 reproduction is arrested by antiretroviral therapy at the same time. Effects which are detrimental to the host are indicated by flash symbols.
Abbreviations: IDO, indoleamine 2,3-dioxygenase; IFN-γ, interferon-γ; 1MT, 1-methyl tryptophan; HIV-1, human immune deficiency virus type 1.

Furthermore, higher neopterin concentrations were significantly correlated with lower levels of vitamins C and E and antioxidant compounds like lutein and zeaxanthin in another study.[93] The data imply a certain ability of such antioxidant compounds to counteract inflammation and immune activation and consequently tryptophan degradation, which could be of benefit in improving mood and cognitive status in patients with HIV-1 infection. However, like 1-methyl tryptophan, such compounds could also reduce the efficacy of the immune response to delay HIV-1 reproduction rates (Figure 4). Interestingly, St John's wort extract is a powerful suppressant of IDO activity and neopterin production in both stimulated and nonstimulated peripheral blood mononuclear cells.[94]

Neuropsychoimmunological biomarkers are not specific for HIV-1 infection

Because of their immunobiological background, the relationship between inflammation and immune activation status and corresponding alterations in biochemical pathways involving tryptophan and serotonin metabolism as well as phenylalanine and tyrosine biochemistry are not specific for patients with HIV-1 infection. Accordingly, significantly enhanced tryptophan degradation as indicated by lowered tryptophan concentrations, together with higher kynurenine and Kyn/Trp levels, have been described in patients with several other infections, mainly of viral origin, and also in patients with sepsis after multiple trauma.[36] Accelerated tryptophan catabolism is also documented in a significant percentage of patients suffering from different types of cancer, leukemia, and lymphoma,[95,96] multiple myeloma,[97] gynecological cancer[98] or autoimmune syndromes, such as rheumatoid arthritis[99] and systemic lupus erythematosus.[100] Most importantly, in patients undergoing treatment with cytokines like interleukin-2 or IFN-γ, enhanced tryptophan degradation is observed,[101,102] which further confirms its link to immune activation-induced biochemical pathways. Elevated Kyn/Trp and lowered tryptophan levels are also common in patients with cardiovascular disease[103,104] and in the blood and CSF of patients suffering from neurodegenerative disorders like Parkinson's disease[105] and Alzheimer's dementia.[106] However, it is also documented during normal ageing that healthy elderly patients have enhanced Kyn/Trp and lower tryptophan concentrations than people of younger age.[107,108] However, the greatest changes in tryptophan metabolism have been observed in patients with HIV-1 infection before HAART, in the late stages of cancer, and in those with sepsis.[109–111]

Phenylalanine metabolism is less widely investigated in groups of patients suffering from diseases and conditions in which inflammation and immune activation play a major role. In addition to HIV-1 infection,[66] an increase in Phe/Tyr and phenylalanine concentrations was observed in patients with multiple trauma and sepsis,[64] cancer[65,112] acute pancreatitis,[113] or hepatitis C virus infection during treatment with IFN-γ.[67] In patients with ovarian cancer, phenylalanine levels and Phe/Tyr have been found to correlate with concentrations of neopterin and 8-isoprostane.[65] Such data support the concept that immune activation and oxidative stress are related to impaired functioning of PAH.[39]

A significant association was observed between lower plasma tryptophan concentrations, increased neopterin concentrations, and impairment of quality of life in patients with colon carcinoma.[114] A similar relationship was found in patients with different kinds of cancer.[115] In patients with multiple myeloma, decreased serum tryptophan levels on treatment with IFN-γ were associated with a greater risk of developing depression.[102,116]

The data support the concept that changes in neuropsychoimmunological biomarkers are not specific for HIV-1 infection, and similar patterns of alterations in neopterin, tryptophan, and phenylalanine metabolism can be detected in any condition associated with immune activation. In particular, accelerated tryptophan degradation is considered

to be involved not only in the greater risk of depressive mood but also in the development of immune dysfunction,[86] anemia[117,118] and weight loss/cachexia,[95,117] which are often observed in patients suffering from diseases featuring inflammation and chronic immune activation. In vitro and animal models are able to support the influence of inflammation and immune activation on tryptophan metabolism and the precipitation of depressive symptoms.[119,120] However, these studies only allow us to conclude that IDO activation plays a major role in the pathogenesis of depression. However, the exact mechanism by which tryptophan and serotonin deprivation versus changes of downstream kynurenine metabolism and altered neuroprotection may contribute to the pathogenesis of major depression remains unresolved.[121]

It is very important to keep in mind that the mechanisms by which altered metabolism of amino acids and consequently of biogenic amines by inflammation and immune activation may contribute to mood changes and neuropsychiatric abnormalities cannot be easily extrapolated to depressive disorders without such an immunological background. Genetic predisposition, like specific polymorphisms of serotonin receptors[122] or immune system functions, can interfere with appropriate tryptophan and serotonin availability and their metabolism, as well as their handling and function as neurotransmitters, eg, single nucleotide polymorphisms of the IFN-γ +874 (T/A) genotype, known to have an effect on IFN-γ production, were found to be associated with kynurenine concentrations and Kyn/Trp in healthy individuals.[123]

Roles of oxidative stress and neopterin

The mechanisms involved in the neurological dysfunction and psychiatric symptoms in patients with HIV-1 infection may include reduced availability of serotonin[49–51] or accumulation of neurotoxins, such as kynurenic acid and quinolinic acid.[43,44] Both circumstances would result from exaggerated tryptophan catabolism. However, the association found between the size of brain lesions, quantified as the ventricle to brain ratio, and neopterin levels may indicate that neopterin itself could be involved in the pathogenesis of brain lesions, because neopterin is capable of enhancing radical-mediated cytotoxic mechanisms[124] and interfering with mitochondrial respiratory chain.[125] Thus, cellular cytotoxicity in immunocompetent cells within the brain might be enhanced in the presence of increased amounts of neopterin. However, neopterin concentrations in serum are more closely related to the extent of brain lesions and the cognitive impairment than CSF levels, as determined by the Structured Interview for the Diagnosis of Alzheimer Dementia score.[16] From such data, it appears that systemic chronic immune stimulation in HIV-1 infection plays a greater role in neurological damage than local CNS phenomena. A more relevant role of systemic metabolic disturbances on the origin of HIV-1-associated neurological impairment might exist, which is probably in addition to local effects of HIV-1 on brain tissue.

Antioxidant vitamins and other antioxidant compounds were found to slow down production of neopterin and IFN-γ as well as tryptophan degradation in human peripheral blood mononuclear cells in vitro. This is most likely due to the fact that pro-oxidants like reactive oxygen species are important forward regulators of the inflammation process, in which induction of nuclear factor κB seems to play a major role. Interestingly, in patients with cardiovascular disease, high serum or plasma neopterin concentrations were strongly correlated with a decline in several antioxidant compounds, such as vitamin C and E, lutein, and zeaxanthin.[93] From these observations, one may conclude that healthy food may allow improvement of mood and neurological impairment in patients. However, in patients with HIV-1 infection, the fear remains that extra antioxidants can also interfere with the antiviral activity of the host immune response.

Discussion

In recent years, a role of immune activation in the pathogenesis of HIV-1 infection has become increasingly recognized,[1–3,126,127] and involvement of disturbed tryptophan metabolism in the development of neurological symptoms has been proposed on several occasions.[17,49,128,129] The biochemical alterations are related to chronic stimulation of macrophages and to production of specific cytokines in the immunoregulatory circuits primarily involved in Th1-type immune activation. IFN-γ activates IDO, which causes degradation of tryptophan, forming kynurenine (Figure 1) and other metabolites,[36] and Kyn/Trp allows an estimate of IDO activity. The consequences of IDO activity are reduced bioavailability of tryptophan for biosynthesis of serotonin and accumulation of toxic compounds, such as kynurenic acid and quinolinic acid. Thus, enhanced induction of tryptophan catabolism by IFN-γ may represent a mechanism relevant to the neurological disturbances present in HIV-1-infected patients.

Tryptophan conversion towards the kynurenine pathway is increased in patients with HIV-1 infection. Because the decline in tryptophan and increase in kynurenine production and Kyn/Trp are closely related to signs of immune activation

in patients, activated IDO appears to be the enzyme responsible for these biochemical alterations. This would make sense, given that the antiviral immune response includes stimulation of several antiproliferative enzymes, amongst which IDO seems to play a major role. Such patients show signs of being immunocompromised because IDO is a negative feedback regulator in the cellular immune response and is related to the induction of regulatory T cells characterized by a forkhead box transcription factor p3 (FOXP3)$^+$ and CD4$^+$/CD25$^+$ phenotype.[126]

Kyn/Trp can serve only as an estimate of IDO activity because kynurenine is an intermediate product within the kynurenine degradation pathway of tryptophan,[43,128] and quinolinic acid also accumulates in body fluids. This is reflected by the fact that alterations in serum/plasma kynurenine concentrations in patients are in the range of 1–3 µmol/L, whereas changes in tryptophan concentrations are approximately 10-fold higher. However, even with these limitations, Kyn/Trp is a reliable readout for tryptophan catabolism. Lowered tryptophan in body fluid concentrations together with enhanced Kyn/Trp justify the conclusion that low tryptophan is not due to reduced dietary intake of this essential amino acid. Correlations between serum IFN-γ and neopterin concentrations on the one hand, and diminished tryptophan levels, increased kynurenine levels, and increased Kyn/Trp on the other,[48,127,130] confirm the relationship between chronic immune activation and enhanced tryptophan catabolism in HIV infection, and also strengthen the conclusion that IDO is very involved in this metabolic peculiarity.

However, when tryptophan degradation and enhanced Kyn/Trp is observed alone and independent of immune activation, it can also be related to enhanced TDO activity, which is induced by steroid hormones like cortisol, and is thus linked to the hypothalamic-pituitary-adrenal axis. This axis is a major part of the neuroendocrine system controlling reactions to stress, and regulates many processes in the human organism, including the immune system and gastrointestinal tract, as well as mood, emotions, and energy balance. In fact, stress and immune responses are closely interrelated (Figure 5). This was also demonstrated by serial neopterin measurements in single case studies reporting that daily life stressors influence urinary neopterin and cortisol levels.[131] Likewise, depression may impact on the course of HIV-1 infection.[132] It is still unclear to what extent a prior influence of stressors on cytokine cascades, in particular IFN-γ, is involved, eg, an influence on IL6 was observed.[133]

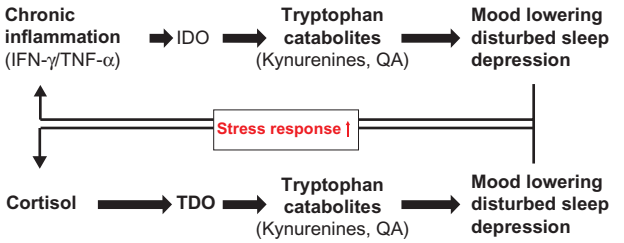

Figure 5 Release of cortisol and the proinflammatory response can cause tryptophan breakdown by IDO and TDO. Proinflammatory cytokines like IFN-γ and TNF-α are involved in induction of IDO during the immune response and lead to tryptophan degradation and accumulation of neurotoxins like QA that may disturb sleep, influence mood, and may precipitate depression. This condition may render patients more vulnerable to stress and consequently enhance the release of cortisol, which may dampen the inflammatory response and can also induce tryptophan degradation and accumulation of neurotoxins like QA by TDO disturbing sleep, influencing mood, and precipitating depression. Obviously this cascade of events can also be initiated by the response to stress.
Abbreviations: IDO, indoleamine 2,3-dioxygenase; IFN-γ, interferon-γ; TDO, tryptophan 2,3-dioxygenase; TNF-α, tumor necrosis factor-α; QA, quinolinic acid.

It remains questionable as to what extent IFN-γ can be induced and detected in the circulation of individuals exposed to stress, but specific antibodies against IFN-γ and TNF-α are able to slow down Kyn/Trp in mice.[133] The measurement of neopterin is more sensitive and reliable than direct measurements of IFN-γ, because this cytokine does not diffuse very well, and if it does, it is rapidly cleared from the plasma and circulation, adhering to soluble cellular or serum receptors, and thus concentrations do not fully correspond to the actual amount of cytokines released. In addition, other cytokines, such as TNF-α, are known to enhance further the effect of IFN-γ on macrophages regarding neopterin production and tryptophan degradation in vitro. In HIV-1 infection, a close relationship exists between IFN-γ, TNF-α, and the neopterin system. However, a correlation does not necessarily indicate a cause-effect relationship.

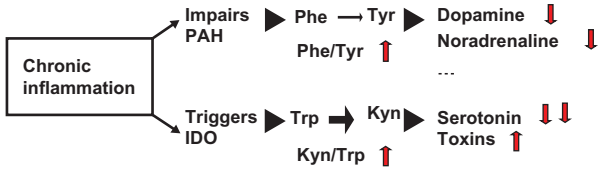

Figure 6 The inflammatory response not only triggers IDO but also impedes the function of phenylalanine hydroxylase. Stimulated IDO and impaired function of PAH both diminish the availability of relevant neurotransmitters like serotonin, dopamine, adrenaline, and noradrenaline, and other neurologically relevant products (indicated by dots). Because the mechanisms involved in the regulation of the IDO (upregulated by proinflammatory cytokines like interferon-γ) and PAH enzymes (most probably downregulated by oxidizing reactive oxygen species) are considerably different, gradual differences in enzyme activities could be important for responses to specific serotonergic or dopaminergic/noradrenergic treatment. The parallel measurement of the kynurenine to tryptophan (Kyn/Trp) and phenylalanine to tyrosine (Phe/Tyr) ratios might provide a basis for decision-making regarding which treatment option is more appropriate for the patient.
Abbreviations: IDO, indoleamine 2,3-dioxygenase; PAH, phenylalanine hydroxylase.

Conclusion

Enhanced tryptophan degradation is observed in HIV-infected patients, and HAART effectively inhibits neopterin formation as well as tryptophan degradation.[80] Thus, effective antiretroviral therapy may not only halt virus replication but also slow down the chronic cellular immune response. Tryptophan, an essential amino acid, is the precursor of serotonin, and decreased availability of both compounds has been postulated to be an important factor in the pathogenesis of mood disturbance and depression.[14] A potential role of impaired PAH activity is also indicated by an increase in Phe/Tyr, which could be of special relevance for neuropsychiatric impairment in patients who do not respond to selective serotonin reuptake inhibitors (Figure 6). Further studies need to be performed with parallel measurements of neopterin, Kyn/Trp, and Phe/Tyr in order to find out whether treatment responses can be predicted by differences between these biomarkers. They may also be useful for identifying treatment-resistant individuals at greater risk of developing chronic depression. However, it will not be easy to make any further recommendations to caregivers from these immunobiological observations except for stringent compliance of patients with antiretroviral therapy. Any specific intervention strategies on, eg, tryptophan breakdown,[87] carry a risk of unforeseen effects on HIV-1 replication, even when an immunological benefit can be expected (see above).

Disclosure

The authors report no conflicts of interest in this work.

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