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## Neopterin production, tryptophan degradation, and mental depression—What is the link?

Bernhard Widner,<sup>a</sup> Andreas Laich,<sup>a</sup> Barbara Sperner-Unterweger,<sup>b</sup>  
Maximilian Ledochowski,<sup>c</sup> and Dietmar Fuchs<sup>a,d,\*</sup>

<sup>a</sup> *Institute of Medical Chemistry and Biochemistry, University of Innsbruck, Fritz Pregl Strasse 3,  
Innsbruck A-6020, Austria*

<sup>b</sup> *Department of Psychiatry, University of Innsbruck, Fritz Pregl Strasse 3, Innsbruck A-6020, Austria*

<sup>c</sup> *Department of Nutritional Medicine, University of Innsbruck, University of Innsbruck, Fritz Pregl Strasse 3,  
Innsbruck A-6020, Austria*

<sup>d</sup> *Ludwig Boltzmann Institute of AIDS Research, University of Innsbruck, Fritz Pregl Strasse 3, Innsbruck A-6020, Austria*

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### Abstract

The cytokine interferon- $\gamma$  stimulates human monocytes/macrophages to release large amounts of neopterin. Increased neopterin concentrations in body fluids of patients are observed during diseases with activated cellular (= TH1-type) immune response such as allograft rejection, virus infections, autoimmune disorders, or malignant tumors but also in neurodegenerative diseases or during pregnancy. In various cells interferon- $\gamma$  induces indoleamine 2,3-dioxygenase (IDO) which degrades tryptophan via the kynurenine pathway. Therefore like increased neopterin formation, enhanced tryptophan degradation is observed in diseases concomitant with cellular immune activation. Disturbed metabolism of tryptophan affects biosynthesis of neurotransmitter 5-hydroxytryptamine (serotonin), and it appears to be associated with an increased susceptibility for depression. In fact, enhanced neopterin concentrations together with increased degradation of tryptophan and low serum levels of tryptophan correlate with neuropsychiatric abnormalities like cognitive decline and depressive symptoms especially in long-lasting and chronic diseases. Activation of IDO could represent an important link between the immunological network and the pathogenesis of depression.

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### 1. Introduction

Major depression is a widespread, and sometimes chronic disorder. Patients suffering from

chronic diseases appear to have an increased risk for developing depression as a consequence of the often impaired future perspectives, but it is also possible that metabolic changes induced by the underlying disease process are critical for psychiatric performance of patients. Recent data indicate several interactions between the immunological networks and neuroendocrine functions. Among them cytokine-induced degradation of

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\* Corresponding author. Fax: +43-512-5072865.

E-mail address: dietmar.fuchs@uibk.ac.at (D. Fuchs).

tryptophan could represent an important aspect, because tryptophan is the precursor for the biosynthesis of 5-hydroxytryptamine (serotonin), a neurotransmitter which appears to play a certain role in depression symptomatology.

## 2. Neopterin

The biosynthesis of neopterin (6-D-erythro-1',2',3'-trihydroxypropylpterin) starts from guanosine triphosphate (GTP) which is converted to 7,8-dihydroneopterintriphosphate by GTP cyclohydrolase I (Fig. 1). Due to a relative deficiency of 6-pyruvoyl-tetrahydropterin synthase, the enzyme required for the conversion of 7,8-dihydroneopterintriphosphate to 5,6,7,8-tetrahydrobiopterin, human monocytes/macrophages on stimulation with interferon- $\gamma$  (IFN- $\gamma$ , a central cytokine within the cellular = Th1-mediated immune response) (Huber et al., 1984) produce and release increased amounts of neopterin at the expense of biopterin derivatives (Fig. 1). Neopterin is found in considerably high concentrations in human body fluids when the cellular immune system is activated. Likewise, measurement of neopterin concentrations allows to sensitively monitor the degree of immune activation (Fuchs, Weiss, & Wachter, 1992, 1993). No specific function of neopterin is known, however, neopterin is able to amplify the activity of reactive oxygen species

(Murr et al., 1994; Wede, Widner, & Fuchs, 1999; Weiss et al., 1993; Widner, Baier-Bitterlich, Wede, Wirleitner, & Fuchs, 1998b). Thus, neopterin may play a role within the defense reaction of the activated monocytes/macrophages by enhancing their pro-oxidative power. In a similar way, neopterin is able to interfere with redox-sensitive intracellular signal-transduction pathways, e.g. inducing the expression of NF- $\kappa$ B (Hoffmann et al., 1996) or triggering apoptosis (Baier-Bitterlich et al., 1995). Accordingly, neopterin concentrations allow an estimate for oxidative stress in vivo (Widner et al., 1998a, 1999), for example, a good correlation has been found in uremia patients between neopterin concentrations in serum and the amount of advanced oxidation products of proteins (Witko-Sarsat et al., 1996). Vice versa, an inverse association exists in serum and cerebrospinal fluid of patients with dementia and in healthy elderly between neopterin and antioxidant vitamin-E ( $\alpha$ -tocopherol) concentrations (Sattler, Leblhuber, Walli, Widner, & Fuchs, 1999).

## 3. Tryptophan degradation

In a variety of cells IFN- $\gamma$  induces the enzyme indoleamine 2,3-dioxygenase (IDO) converting tryptophan into *N*-formylkynurenine which is subsequently deformed to kynurenine (Fig. 2) (Taylor & Feng, 1991). The ratio of concentrations

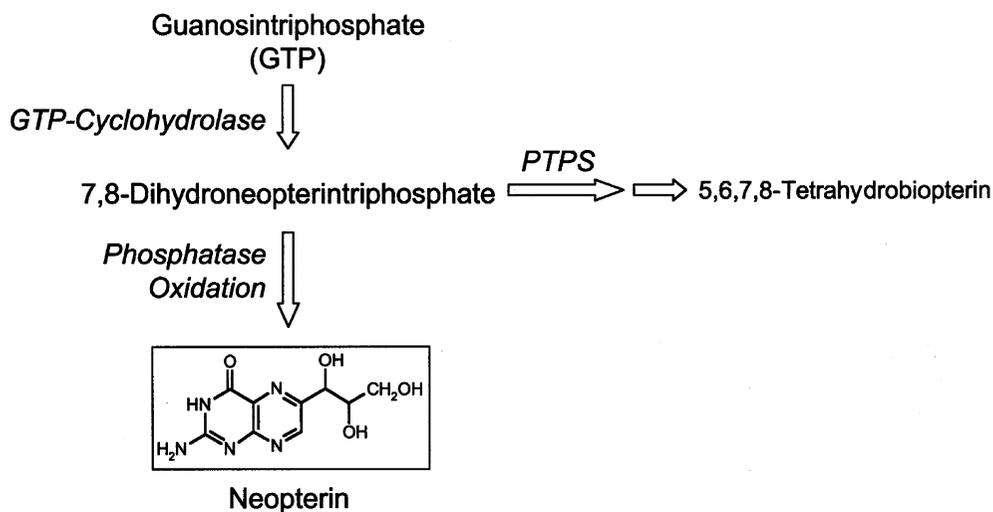


Fig. 1. Biosynthesis of neopterin (6-D-erythro-1',2',3'-trihydroxypropylpterin): guanosine triphosphate (GTP) is converted by GTP-cyclohydrolase I to 7,8-dihydroneopterin, the precursor molecule of 5,6,7,8-tetrahydrobiopterin. Due to a relative deficiency of 6-pyruvoyl-tetrahydropterinsynthase (PTPS) in human monocytes/macrophages, neopterin accumulates at the expense of biopterin derivatives.

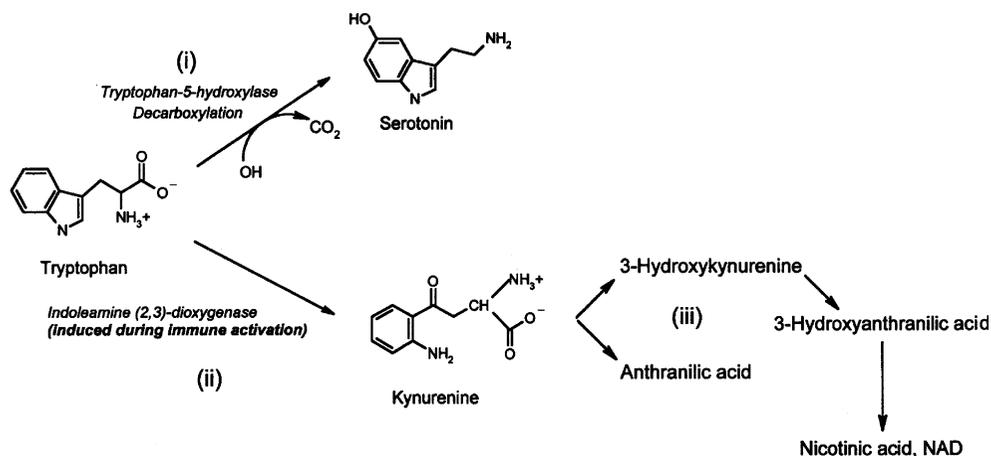


Fig. 2. Tryptophan is metabolized mainly via two biochemical routes: (i) by tryptophan-(5)-hydroxylase and subsequent decarboxylation it is converted to the neurotransmitter serotonin, (ii) by tryptophan-pyrrolase and indoleamine-2,3-dioxygenase it is transformed to kynurenine which is further converted (iii) to several metabolites on the way to nicotinic acid dinucleotides.

of the first product kynurenine and the substrate of IDO, tryptophan, can serve as an estimate for the activity of IDO (Fuchs et al., 1990). Tryptophan is an essential amino acid and is important for protein synthesis and also for the biosynthesis of the neurotransmitter 5-hydroxytryptamine (= serotonin). Consequently, immunologically induced tryptophan degradation may elicit neuropsychiatric symptoms when the availability of tryptophan is insufficient for normal serotonin biosynthesis (Maes et al., 1993; Price, Malison, McKougle, Pelton, & Heninger, 1998; Song et al., 1998; Widner, Wirleitner, Baier-Bitterlich, Weiss, & Fuchs, 2000b). In addition, certain neuroactive catabolites of tryptophan may be formed from cells when tryptophan is degraded (Freese, Swartz, During, & Martin J.B, 1990).

In activated immunocompetent cells, IDO-induced tryptophan degradation seems to be part a defence mechanism to prevent growth of, e.g., intracellular pathogens (Pfefferkorn, 1984) or malignant cells (de la Maza & Peterson, 2000; Ozaki, Edelstein, & Duch, 1988) by withdrawing the essential amino acid tryptophan from a micro-environment. Tryptophan degradation by monocytes/macrophages may also slow down T-cell response (Munn et al., 1998, 1999).

In various diseases decreased tryptophan together with increased kynurenine and an increased kynurenine per tryptophan ratio is found, the latter indicating that low tryptophan resulted from enhanced degradation rather than reduced

dietary intake (Fuchs et al., 1990). In addition, a close association exists between the rate of tryptophan degradation and serum neopterin as well as other markers of cellular immune activation like soluble tumour necrosis factor receptor and soluble interleukin-2 receptor (Widner et al., 2000b).

### 3.1. Neopterin and tryptophan degradation in human diseases

Increasing neopterin concentrations in allograft recipients indicate rejection episodes or infectious complications early. In autoimmune diseases like rheumatoid arthritis and systemic lupus erythematosus increased neopterin concentrations correlate with the disease activity, and increased neopterin concentrations were found during pregnancy (Fuchs et al., 1992) and also in neurodegenerative diseases like Alzheimer's and Huntington's disease (Leblhuber et al., 1998, 1999). In malignant diseases (Murr et al., 1999) as well as in HIV infected individuals (Fahey et al., 1990; Fuchs et al., 1992) higher neopterin concentrations are associated with shorter survival. Neopterin measurements are also useful for screening of blood donations to exclude potentially hazardous pathogens (Hönlinger et al., 1989).

The spectrum of diseases in which increased degradation of tryptophan has been described is very similar to the one with increased neopterin

production (Widner et al., 2000b): lowered tryptophan, increased kynurenine, and an increased kynurenine per tryptophan ratio are common in patients with infections including HIV infection, in patients with systemic lupus erythematosus (Widner et al., 2000a) and malignancies and also during pregnancy (Denz et al., 1993; Maloney, St. Claire, Widner, Werner, & Fuchs, 2000; Schröcksnadel, Baier-Bitterlich, Dapunt, Wachter, & Fuchs, 1996). In patients with HIV infection and in adult T-cell leukaemia, low tryptophan concentrations were predictive for more rapid disease progression and earlier death (Fahey et al., 1990; Maloney et al., 2000). Finally, increased production of neopterin and degradation of tryptophan have been demonstrated in patients with depression (Maes et al., 1993).

### 3.2. Neopterin, tryptophan degradation, and neuropsychiatric presentation of patients

In HIV infection, highest neopterin concentrations in serum and cerebrospinal fluid are found in patients with AIDS-associated dementia (Brew, Dunbar, Pemberton, & Kaldor, 1996). Moreover, high neopterin concentrations coincide with impaired cognitive ability of the patients (Fuchs et al., 1989). In a similar way, tryptophan degradation and low tryptophan levels in patients with HIV infection are associated with impaired cognitive performance (Fuchs et al., 1990). In patients with malignancy high neopterin and low tryptophan concentrations are not only predictive for poor survival (Murr et al., 1999), they also correlate with the quality of life score in patients (Huang et al., 2002). In patients with Alzheimer's and with Huntington's disease, patients with more reduced mental performance present with higher neopterin concentrations and there exists an inverse correlation between serum neopterin levels and Mini-Mental-Scores, MMS (Leblhuber et al., 1998, 1999). Immune activation in the peripheral blood of patients with Alzheimer's disease and Huntington's disease is also evident by enhanced degradation of tryptophan (Leblhuber et al., 1998; Widner et al., 2000c). The kynurenine per tryptophan ratio in Alzheimer's disease and Huntington's disease are related to MMS, patients with lower cognitive performance presenting with a higher rate of tryptophan degradation and lower tryptophan concentrations, and in patients with Huntington's disease higher neopterin and lower tryptophan concentrations are also predictive for shorter survival.

## 4. Conclusion

Neopterin concentrations and the tryptophan degradation rate, as indicated by the kynurenine per tryptophan ratio, serve as markers for cellular immune activation concomitant with enhanced IFN- $\gamma$  formation. Tryptophan catabolism is actually increased in patients suffering from various disorders and it further closely correlates with the serum concentrations of neopterin and other markers of immune activation.

Low tryptophan concentrations due to IDO-induced degradation may lead to serotonin depletion and hence to serotonergic dysfunctions. This association is evident in various diseases linked with an activated immune system. In these situations close correlations between serum kynurenine per tryptophan ratios and neopterin concentrations are found. Interestingly, also decreased serotonin concentrations are common in the blood of patients with malignant disease and with HIV infection (Launay et al., 1988, 1989).

Increased neopterin and decreased tryptophan concentrations are found to predict poor prognosis in patients with cancer and with malignant diseases. Thus in case when a depressive disorder is developing in such a patient, it could be a result of reduced tryptophan and thus limited serotonin availability due to increased immune activation

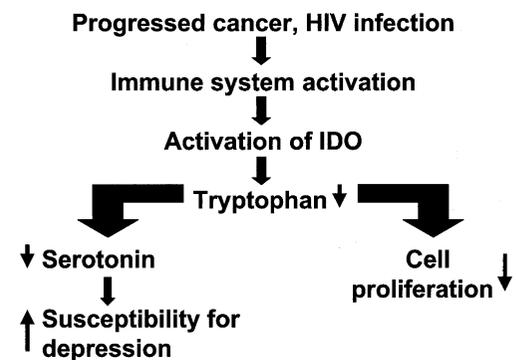


Fig. 3. Depressive symptoms as a result of immune system activation: patients with poor prognosis suffering from certain malignancies or from HIV infection present with an increased rate of tryptophan degradation. Enhanced tryptophan catabolism due to cytokine-induced indoleamine (2,3)-dioxygenase (IDO) decreases tryptophan availability intended to reduce cell proliferation. Decreased tryptophan availability also limits the biosynthesis of serotonin and thereby may increase the susceptibility for depression in patients with poor prognosis.

and stimulation of IDO preferentially in patients with reduced survival expectations (Murr et al., 2000; Fig. 3). Notably, correlations described not necessarily confirm a cause–effect relationship. However, the finding that tryptophan depletion produces a relapse of symptoms in patients with depression who have responded to treatment with antidepressants (Bell, Abrams, & Nutt, 2001) further suggests that serotonin function is important in the pathogenesis of this condition.

In conclusion, immune system activation is associated with enhanced degradation of tryptophan. As a consequence, availability of tryptophan for the biosynthesis of serotonin is reduced and may represent the basis for the development of depressive disorders in patients with various immunopathologies, especially in chronic diseases.

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