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Review

Neopterin as a potential cytoprotective brain molecule

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ABSTRACT

Neopterin, a byproduct of the tetrahydrobiopterin *de novo* pathway, is found in increased levels in cerebrospinal fluid and plasma and significantly increases upon damage, infection or during immune system activation. The production of this compound seems almost restricted to the monocyte/macrophage linage cells, in response to interferon-γ stimulation. However, it is unclear whether and which nervous cells are able to synthesize neopterin, respond to any stressor applied extracellularly, or even the role of the compound in the central nervous system. Here we propose a potential cytoprotective role of neopterin in the brain, and show evidence that cultured rat astrocytes are responsive to the molecule; the pterin elicited increased hemeoxygenase-1 cellular content and decreased oxidative stress induced by mitochondrial dysfunction. Further studies are needed to clarify neopterin's cytoprotective effects in the central nervous system, and its potential role in different neuroinflammatory diseases.

Contents

1. Background

Increased plasma neopterin is widely considered to be a sensitive biomarker for cell-mediated immune activation in several conditions, including viral infections, certain malignancies, allograft rejection, autoimmune and neurodegenerative diseases (Fuchs et al., 1989b; Widner et al., 2002; Wirleitner et al., 2002; Parker et al., 2013). Neopterin is a byproduct of the tetrahydrobiopterin (BH4) biosynthetic pathway, which requires Mg^{2+}, Zn^{2+} and NADPH as cofactors. BH4 is an obligatory cofactor for phenylalanine, tyrosine, tryptophan hydroxylases and alkylglycerol monooxygenase (Werner et al., 2011), and for all isoforms of nitric oxide synthase (NOS) (Mayer et al., 1990). BH4 is synthesized by multiple metabolic routes, namely the *de novo*, salvage and recycling pathways. The *de novo* via generates BH4 from guanosine triphosphate (GTP) by the concert action of guanosine triphosphate cyclohydrolase I (EC 3.5.4.16; GTPCH), 6-pyruvoyl tetrahydropterin synthase (EC 4.6.1.12; PTPS) and sepiapterin reductase (EC 1.1.1.153; SR) (Thony et al., 2000). GTPCH catalyzes the conversion of GTP to

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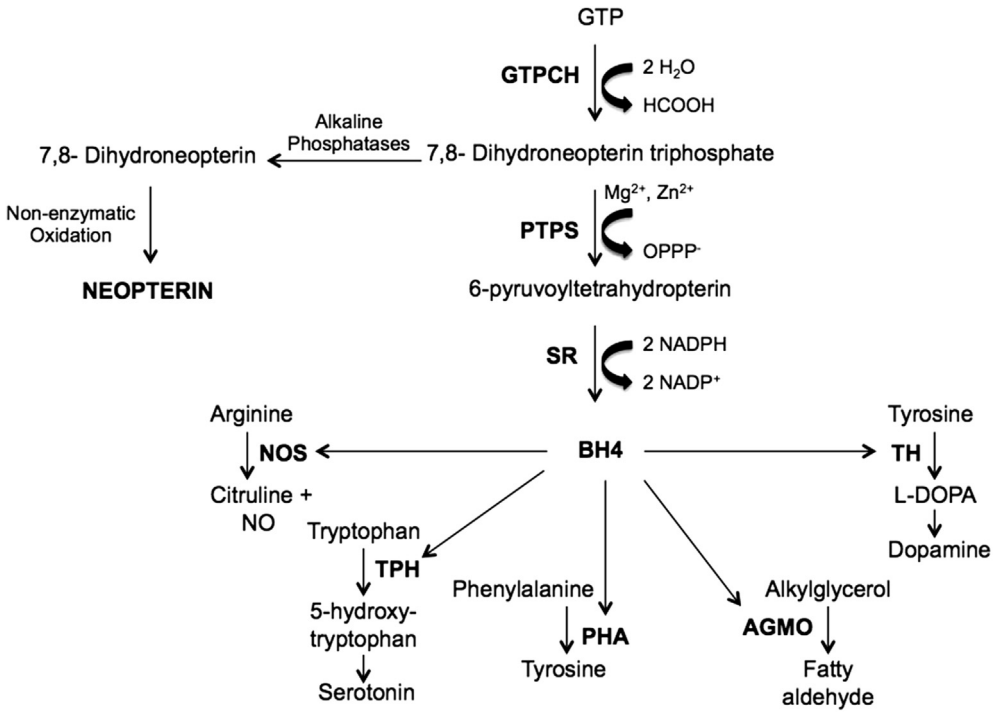

Fig. 1. Neopterin synthesis through the tetrahydrobiopterin (BH4) *de novo* biosynthetic pathway. Guanosine triphosphate (GTP), GTP cyclohydrolase I (EC 3.5.4.16; GTPCH), 6-pyruvoyl-tetrahydropterin synthase (EC 4.6.1.12; PTPS), and sepiapterin reductase (EC 1.1.1.153; SR), nitric oxide synthase; all isoforms (EC 1.14.13.39; NOS), tryptophan hydroxylase (EC 1.14.16.4; TPH), phenylalanine hydroxylase (EC 1.14.16.1; PAH); tyrosine hydroxylase (EC 1.14.16.2; TH), alkylglycerol monooxygenase (E.C. 1.14.16.5; AGMO), nitric oxide (NO).

7,8-dihydroneopterin triphosphate (Blau et al., 1989; Werner et al., 1990; Millner et al., 1998). Then, PTPS removes the phosphates to generate 6-pyruvoyl-tetrahydropterin, which is further converted to BH4 by SR (Werner et al., 1990).

GTPCH is the rate-limiting enzyme of the *de novo* pathway (Levine et al., 1990), and it is known to be transcriptionally regulated by interferon-γ (IFN-γ), interleukin-1beta (IL-1β) (Franscini et al., 2003), tumor necrosis factor alpha (TNFα) (D'Sa et al., 1996), nerve growth factor (NGF) (Bauer et al., 2002) and hydrogen peroxide (H_2O_2) (Ishii et al., 2005) levels, among others. While GTPCH activity can be stimulated up to 100-fold, PTPS and SR remain slightly increased under inflammatory conditions (Kerler et al., 1989; Werner et al., 1990; Werner-Felmayer et al., 1993a). Then, PTPS becomes the rate-limiting enzyme during BH4 biosynthesis (Werner et al., 1990; Werner-Felmayer et al., 1993b). This is especially true for human monocytes/macrophages since these cells are relatively scarce in PTPS (Werner et al., 1990). However, in murine monocytes/macrophages or human neuronal cells, in which PTPS expression is usually present, biopterin (the highest oxidation state of BH4) production will be favored and lower levels of neopterin will accumulate (Werner-Felmayer et al., 1993b) (Fig. 1).

1.1. Neopterin is a peripheral early biomarker of cellular immune response

Neopterin is a recognized biomarker for immune system activation. IFN-γ, which is released from activated Th1 cells during the initiation of the immunological cellular response, is one of the main stimuli for neopterin formation (Fuchs et al., 1989b; Cano et al., 2008; Molero-Luis et al., 2013). Under these conditions, activated immune cells, including monocytes, macrophages or dendritic cells, up-regulate inducible NOS (NOS2) in order to elicit the synthesis of nitric oxide (NO). The consequent increased NOS2 activity for sustaining NO production requires higher concentrations of cofactors, including the mandatory cofactor BH4. To couple these processes, GTPCH is also upregulated through positive feedback, overpassing the PTPS capacity and leading to the accumulation of 7,8-dihydroneopterin triphosphate, with the posterior non-enzymatic conversion to neopterin (Thony et al., 2000; Schairer et al., 2012). Once produced, neopterin is considered a sensitive and early marker of the inflammatory response and its concentration increase in fluids such as plasma or cerebrospinal fluid (CSF) (Huber et al., 1984; Wirleitner et al., 2002). The expected value for plasma or serum and also CSF neopterin in healthy adult subjects is about 5–8 nmol/L (Hagberg et al., 1993; Widner et al., 2002; Casal et al., 2003; Kuehne et al., 2013; Hytonen et al., 2014). These values are at least 2- to 3-fold higher in pathological conditions characterized by immune system activation. For instance, neopterin reaches more than 15 nmol/L in plasma and 10 nmol/L in CSF from non-treated HIV patients (Suh et al., 2014) and nearly 16 nmol/L in plasma from Alzheimer's disease patients in advanced stages of dementia (Wissmann et al., 2013). Furthermore, the metabolite could reach about 500 nmol/L in the CSF (Blau et al., 1996; Opladen et al., 2012) in a genetically-driven metabolic disease characterized by PTPS deficiency (Niederwieser et al., 1979).

1.2. Origin of CNS neopterin

The source of neopterin in the central nervous system (CNS) is not well understood. The evidence available in the literature has suggested that neopterin crosses the blood–brain barrier, therefore the CSF levels may reflect the serum or plasma neopterin concentrations (Fuchs et al., 1989a). However, this process is thought to occur with a very low quotient (1/40) (Hagberg et al., 1993). Moreover, neopterin levels are higher in the CSF than in plasma or serum in severe traumatic brain injury (Lenzlinger et al., 2001) or