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Review

Inflammation, vitamin B6 and related pathways

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ABSTRACT

The active form of vitamin B6, pyridoxal 5′-phosphate (PLP), serves as a co-factor in more than 150 enzymatic reactions. Plasma PLP has consistently been shown to be low in inflammatory conditions; there is a parallel reduction in liver PLP, but minor changes in erythrocyte and muscle PLP and in functional vitamin B6 biomarkers. Plasma PLP also predicts the risk of chronic diseases like cardiovascular disease and some cancers, and is inversely associated with numerous inflammatory markers in clinical and population-based studies. Vitamin B6 intake and supplementation improve some immune functions in vitamin B6-deficient humans and experimental animals. A possible mechanism involved is mobilization of vitamin B6 to the sites of inflammation where it may serve as a co-factor in pathways producing metabolites with immunomodulating effects. Relevant vitamin B6-dependent inflammatory pathways include vitamin B6 catabolism, the kynurenine pathway, sphingosine 1-phosphate metabolism, the transsulfuration pathway, and serine and glycine metabolism.

Contents

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1. Introduction

Vitamin B6 is a generic name that includes three different pyridine derivatives modified at their 4-position and denoted pyridoxal (PL), pyridoxamine (PM) and pyridoxine (PN), carrying an aldehyde, aminomethyl and hydroxymethyl group, respectively. All three forms exist as derivatives that are phosphorylated at the 5-position. These are pyridoxal 5′-phosphate (PLP), pyridoxamine 5′-phosphate (PMP) and pyridoxine 5′-phosphate (PNP) (Coburn, 1996). The structure and metabolism of B6 vitamers are summarized in Fig. 1.

PLP is not synthesized *de novo* in humans, but is obtained from various foods including meat, milk products, beans, nuts, potatoes and several fruits and vegetables. Animal products mostly contain PLP and PMP, whereas in plant-derived products, PN(P) is the prevailing/principal B6 form. Ingested PLP, PMP and PNP are dephosphorylated by the ecto-enzyme tissue-specific intestinal phosphatase, prior to absorption. The portal circulation delivers PL, PM and PN to the liver, where they are rephosphorylated by pyridoxal kinase (PDXK), and PMP and PNP are converted to PLP in reactions catalyzed by pyridoxine (pyridoxamine) oxidase (PNPO) (Albersen et al., 2013; Coburn, 2015). In the liver, PLP production is regulated (Merrill et al., 1978) such that the content remains relatively constant, even after a very high intake of PN (Schaeffer et al., 1989). The liver is also the production site of PLP destined for release into plasma (Huang et al., 2012; Lumeng et al., 1974), which in addition to PLP (about 70–80%) contains PL (8–30%) and the

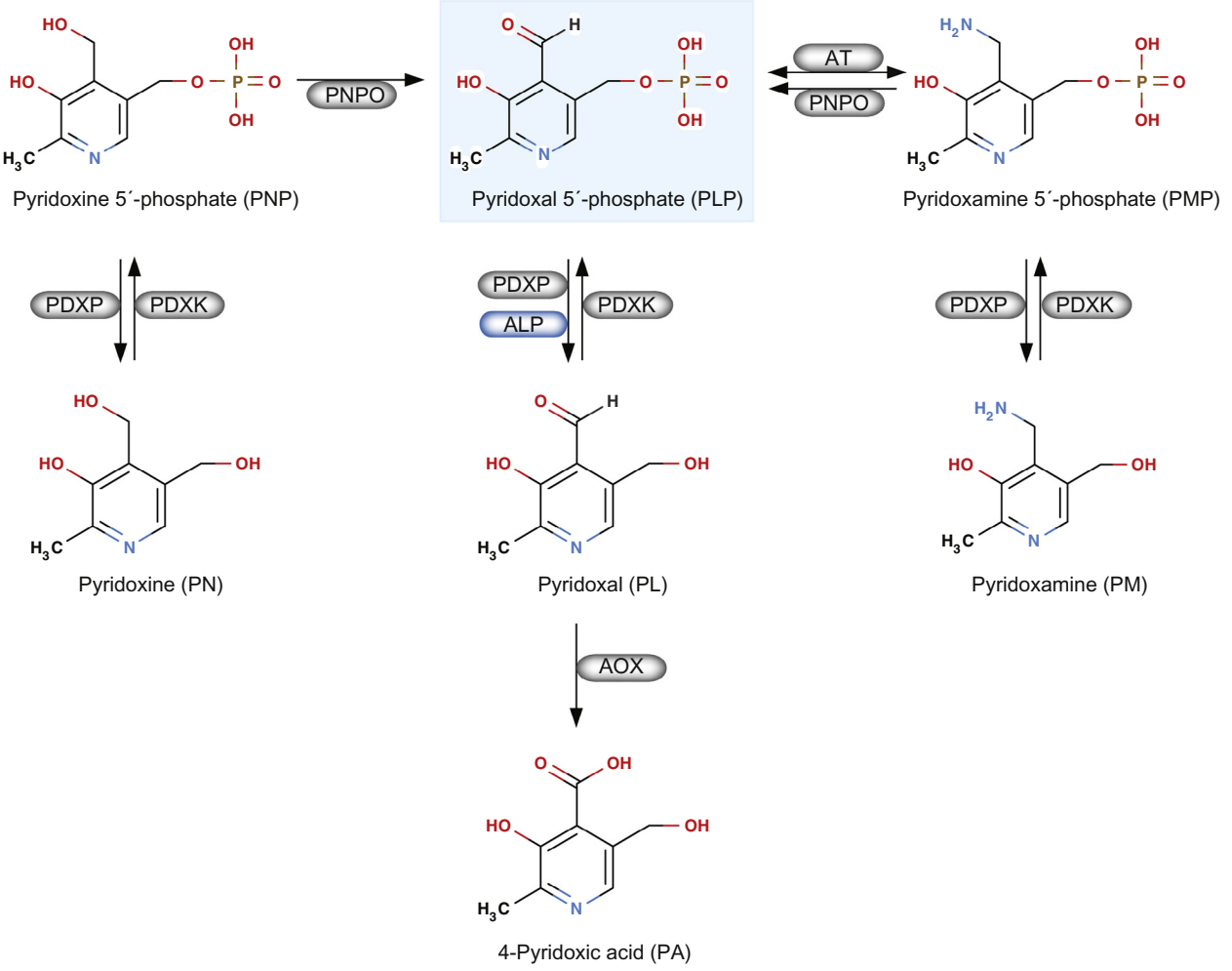

Fig. 1. Vitamin B6 forms, metabolism and the enzymes involved. Pyridoxal 5′-phosphate (PLP) is the metabolically active co-enzyme form of vitamin B6, pyridoxal (PL) is the transport form that crosses biological membranes, pyridoxine (PN) the vitamin B6 species present in supplements, and 4-pyridoxic acid (PA) is the vitamin B6 catabolite. PL, PN, and pyridoxamine (PM) are phosphorylated by pyridoxal (pyridoxine, vitamin B6) kinase (PDXK; EC 2.7.1.3511) to PLP, pyridoxine 5′-phosphate (PNP), and pyridoxamine 5′-phosphate (PMP), respectively. PNP and PMP are oxidized to PLP in reactions catalyzed by pyridoxamine 5′-phosphate oxidase (PNPO; EC 1.4.3.5). PLP in the liver is bound to albumin and is exported into the circulation for delivery to tissues. Before cellular uptake, extracellular PLP is dephosphorylated to PL by the ectoenzyme, tissue-nonspecific alkaline phosphatase (ALP; EC 3.1.3.1). Dephosphorylation of PLP to PL is also catalyzed by the intracellular enzyme, pyridoxal (pyridoxine, vitamin B6) phosphatase (pyridoxal phosphate phosphatase, PDXP; EC 3.1.3.74). The irreversible oxidation of PL to PA is catalyzed by aldehyde oxidase(s) (AOX). Abbreviation: AT, aminotransferase. Modified from Ueland et al. (2015).

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vitamin B6 catabolite, 4-pyridoxic acid (PA) (Leklem, 1990; Talwar et al., 2003). PLP is exported from the liver bound to albumin. In plasma, PLP remains tightly bound to albumin (Huang et al., 2012; Lumeng et al., 1974) and increases over a broad range of vitamin B6 intake (Hansen et al., 1997, 2001). Plasma PLP must be dephosphorylated to the transport form, PL, before being taken up by tissues or cells or passing the blood–brain barrier. The dephosphorylation is catalyzed by tissue-specific phosphatases, expressed in placenta and germ cells, and the tissue-nonspecific alkaline phosphatase (ALP), which is an ectoenzyme located on the outer membrane of cells, including erythrocytes (Buchet et al., 2013).

PLP, the active B6 vitamer, serves as co-factor for more than 150 enzymes, which constitute about 4% of all enzyme activities (Percudani and Peracchi, 2009). These enzymes catalyze a wide range of reactions involving amino acids and amines, including transaminations, aldol cleavages, α-decarboxylations, racemizations, β- and γ-eliminations, and replacement reactions (Eliot and Kirsch, 2004). Most reactions are part of amino acid synthesis and degradation, while others are related to one-carbon metabolism, lipid metabolism, gluconeogenesis, heme and neurotransmitter biosynthesis (Eliot and Kirsch, 2004; Percudani and Peracchi, 2009). As well as functioning as a co-factor, vitamin B6 has been described as a scavenger of reactive oxygen species (Kannan and Jain, 2004), metal chelator (Wondrak and Jacobson, 2012) and chaperone in the enzyme folding process (Cellini et al., 2014).

2. Vitamin B6 status and diseases

Isolated dietary vitamin B6 deficiency is rare in developed countries, but low circulating vitamin B6 has been reported in users of oral contraceptives or some drugs (Spinneker et al., 2007), in smokers (Ulvik et al., 2010), and in subjects with alcoholism (Ulvik et al., 2010), coeliac disease or diabetes (da Silva et al., 2012). Low vitamin B6 intake is associated with increased risk of cardiovascular disease (Rimm et al., 1998; Tavani et al., 2004) and cancer in some (Lim et al., 2005; Theodoratou et al., 2008; Wei et al., 2005) but not all (Larsson et al., 2010; Zhang et al., 2013) prospective studies. In general, the observed associations between low circulating PLP and risk of chronic diseases are generally more consistent (Page et al., 2009; Zhang et al., 2013), which may reflect a rather weak relation between vitamin B6 intake and plasma PLP (Larsson et al., 2010; Rimm et al., 1998).

Low plasma PLP has been associated with risk of cardiovascular disease (Cheng et al., 2008; Dalery et al., 1995; Folsom et al., 1998; Friso et al., 2004; Page et al., 2009; Robinson et al., 1998; Vanuzzo et al., 2007; Verhoef et al., 1996), stroke (Kelly et al., 2003, 2004) and venous thrombosis (Hron et al., 2007) in several, including three prospective studies (Folsom et al., 1998; Page et al., 2009; Vanuzzo et al., 2007). However, it has been conjectured that systemic inflammation, as measured by elevated C-reactive protein (CRP), accounts for the prediction of myocardial infarction by plasma PLP (Dierkes et al., 2007). Prospective associations have also been observed between low plasma PLP and several cancers, including cancer of the ventricle (Eussen et al., 2010), colorectum (Larsson et al., 2010; Le Marchand et al., 2009; Lee et al., 2009), lung (Johansson et al., 2010), breast (Lurie et al., 2012; Wu et al., 2013) and kidney (Johansson et al., 2014). In patients with established kidney cancer, high plasma PLP was associated with lower mortality (Muller et al., 2015). Low plasma PLP has also been linked to rheumatoid arthritis (RA) (Chiang et al., 2005; Huang et al., 2010; Roubenoff et al., 1995), inflammatory bowel disease (IBD) (Selhub et al., 2013), and diabetes (Friedman et al., 2004). As with cardiovascular disease and cancer, these are all conditions where inflammation is believed to play a key role in pathogenesis or disease progression (de Visser et al., 2006; Hansson et al., 2006; Tan et al., 2010).

In patients with IBD (Saibeni et al., 2003) or RA (Chiang et al., 2003a, 2003b), plasma PLP was inversely associated with the severity of the disease. RA patients had normal erythrocyte PLP but low plasma PLP (Chiang et al., 2005), that was not explained by low B6 intake, congenital defects in vitamin B6 metabolism (Chiang et al., 2003b; Paul et al., 2013) or vitamin B6 deficiency, as judged by a panel of functional vitamin B6 biomarkers (Chiang et al., 2003a, 2003b; Roubenoff et al., 1995). An experimental study in rats with adjuvant arthritis showed that affected animals had low plasma PLP, which correlated with low liver PLP, whereas the PLP content in muscle, the major PLP pool, was not affected (Chiang et al., 2005). Furthermore, urinary PA excretion was not increased in RA patients and rats with adjuvant arthritis, suggesting no excessive vitamin B6 catabolism (Chiang et al., 2005).

Vitamin B6 status in critically ill patients as assessed by a transaminase activation assay and vitamin B6 intake were similar to these parameters in healthy controls (Huang et al., 2005), but the patients had reduced plasma PLP, elevated plasma PA (Huang et al., 2005), and normal (Quasim et al., 2005) or slightly reduced (Vasilaki et al., 2008) erythrocyte PLP; both plasma PLP and PA were associated with indices of immune response (Huang et al., 2005). Similarly, in patients with myocardial infarction, plasma PLP showed a transient 40% fall with a nadir at about 40 hours after admission; the decline was accompanied by an equivalent increase in erythrocyte PLP. Plasma PLP returned to normal levels whereas erythrocyte PLP stayed elevated at the time of discharge (Vermaak et al., 1988). Supplementation of critically ill patients who had systemic inflammation with high dose pyridoxine caused no (Quasim et al., 2005) or a slight increase in plasma PLP (Cheng et al., 2006), a moderate (3-fold) increase in erythrocyte PLP (Quasim et al., 2005), and a drastic (15–20 fold) increase in plasma PL (Cheng et al., 2006).

3. Vitamin B6, immune function and inflammation

Vitamin B6 deficiency affects cell-mediated immunity and to a lesser extent humoral immunity in both animal and human studies (Chandra and Sudhakaran, 1990; Rall and Meydani, 1993). A profound reduction in lymphocyte proliferation, T-cell mediated cytotoxicity, delayed-type hypersensitivity, allograft rejection (Rall and Meydani, 1993) and altered cytokine profile (Doke et al., 1998) have been demonstrated in experimental studies on vitamin

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B6-deficient rodents. Immune response in elderly subjects (Talbott et al., 1987), patients with renal failure (Casciato et al., 1984), and critically ill patients (Cheng et al., 2006) is improved by supplementation with pyridoxine. The immune responses in elderly (Meydani et al., 1991), and in young women (Kwak et al., 2002) have been investigated in well-controlled metabolic settings as a function of variable vitamin B6 status. In the elderly, vitamin B6 depletion decreased the number and mitogen response of blood lymphocytes, in particular T-helper cells, and interleukin (IL) 2 production. The immune indices were normalized upon vitamin B6 repletion (Meydani et al., 1991). In young women consuming 1 mg vitamin B6 per day (slightly below the recommended RDA of 1.3 mg/day) for one week, lymphocyte proliferation (but not IL-2 production) increased in a dose-dependent manner as a function of vitamin B6 intake up to 2.1 mg/day. This suggests that vitamin B6 intake higher than the current RDA is required for maximum *ex vivo* lymphocyte mitogen response (Kwak et al., 2002).

4. Vitamin B6 and markers of inflammation

Plasma PLP shows an inverse association with inflammatory markers in clinical (Friedman et al., 2004; Friso et al., 2004; Huang et al., 2005; Saibeni et al., 2003; Ulvik et al., 2012) and population-based studies. Studies on population-based cohorts have demonstrated that plasma PLP is inversely related to numerous markers of inflammation, including CRP (Friso et al., 2001; Morris et al., 2010; Shen et al., 2010), IL-6 receptor (Gori et al., 2006), α-1-antichymotrypsin (Bates et al., 1999a, 1999b), serum amyloid A (Abbenhardt et al., 2014), white blood cell count (WBC), kynurenine/tryptophan ratio (KTR), neopterin (Midttun et al., 2011; Theofylaktopoulou et al., 2014), and to an overall inflammatory summary score and summary scores representing different inflammatory modalities (Sakakeeny et al., 2012).

In the population based NHANES study (Morris et al., 2010), vitamin B6 intake from diet and supplements was inversely associated with CRP. Higher intake but also adequate plasma PLP (>20 nmol/L) independent of intake appeared to protect against inflammation. Among subjects with vitamin B6 intake of 2–3 mg/d, vitamin B6 inadequacy (plasma PLP < 20 nmol/L) was uncommon (10%) in individuals with low CRP (≤3 mg/ML) but occurred more frequently (50%) in individuals with high CRP (>10 mg/L). These results could be obtained both if vitamin B6 protects against inflammation and if inflammation adversely affects vitamin B6 status as measured by plasma PLP (Morris et al., 2010). Notably, in a small study on healthy individuals, controlled dietary vitamin B6 restriction did not affect the CRP levels (Davis et al., 2006), and in patients with stable angina pectoris, levels of inflammatory markers like CRP, neopterin or soluble CD40 ligand were not changed following supplementation with high-dose (40 mg/d) PN alone or in combination with folic acid and vitamin B12 (Bleie et al., 2007). A strong inverse association between CRP and plasma PLP was maintained in cardiovascular patients even after supplementation (Ulvik et al., 2012). Thus, intervention studies suggest that the inverse association between CRP and plasma PLP reflects altered vitamin B6 distribution during inflammation rather than high B6 protecting against inflammatory reactions.

Plasma PLP was inversely associated with CRP, WBC, KTR and neopterin, whereas PA showed a positive association with neopterin and KTR in patients with stable angina pectoris. These associations were essentially upheld after supplementation with high dose pyridoxine for 28 days. After supplementation, all B6 vitamers were increased 9–60-fold, but there was a steep drop in PL and PA in subjects with CRP > 7 mg/L (Ulvik et al., 2012). These data suggest that acute-phase reaction (reflected by elevated CRP) leads to increased uptake of vitamin B6 into tissues whereas cellular Th1 immune activation (neopterin and KTR) promoted uptake and a concurrent catabolism to PA.

5. B6 catabolism and the PAr index

4-Pyridoxic acid (PA) is a vitamin B6 catabolite formed in the liver from PL (Merrill et al., 1984). PA in plasma is increased after vitamin B6 intake (Bates et al., 1999a, 1999b; Hansen et al., 2001), is not protein-bound (Anderson et al., 1974), has high renal clearance and is excreted in the urine (Coburn et al., 2002; Zempleni and Kübler, 1995). PA, as opposed to PLP, is not related to acute-phase inflammatory status in the general population (Bates et al., 1999a, 1999b), but is positively related to markers of cellular immune activation (Ulvik et al., 2012) and is markedly increased in critically ill patients (Huang et al., 2005).

The major circulating B6 vitamers, PLP, PL and PA, are measured simultaneously by contemporary methods based on mass spectrometry (Midttun et al., 2009), and demonstrate a strong intercorrelation (Bor et al., 2003; Midttun et al., 2007), which may reflect tight metabolic control. The ratio PA/(PLP + PL), termed PAr index, was selected from other possible B6 vitamer combinations based on its high within-subject reproducibility (ICC of 0.75) (Ulvik et al., 2014), which suggests that PAr reflects key processes related to an individual's vitamin B6 homeostasis.

PAr has some unique characteristics. Compared to the isolated B6 vitamers in plasma, PAr is less influenced by renal function, smoking, and vitamin B6 intake (Ulvik et al., 2014). Approximately 90% of the explained variance of PAr is accounted for by a summary score that includes four inflammatory markers (CRP, WBC, KTR and neopterin), and PAr efficiently discriminates high inflammatory status in ROC analyses (AUC of 0.85) (Ulvik et al., 2014).

The PAr response can be dissected into changes in PA, PL and PLP according to CRP and markers of cellular immunity (KTR and neopterin). PA was positively related to KTR and neopterin but not to CRP, whereas PLP and PL were more strongly associated with CRP than with KTR and neopterin (Ulvik et al., 2014). These observations suggest that during acute phase (reflected by CRP) there is increased uptake of PLP and PL, whereas cellular immune activation is dominated by increased PL degradation to PA. Thus, the PAr index is a measure of both these inflammatory modalities.

Cellular uptake of vitamin B6 includes dephosphorylation of PLP to PL, which crosses the cell membrane, and is retained within the cells after rephosphorylation to PLP catalyzed by PL kinase (di Salvo et al., 2011). PLP and PL are interconvertible, and PLP-specific phosphatases exist in most

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tissues (Jang et al., 2003). The oxidation of PL to PA is irreversible and is believed to be catalyzed by liver Aldehyde oxidase 1 (AOX 1) (Garattini et al., 2009; Merrill et al., 1984), the expression of which is regulated by oxidative stress-related signal pathways (Maeda et al., 2012). PL is also oxidized to PA by aldehyde dehydrogenase (ALDH), which is expressed in many tissues (Stanulović et al., 1976). Thus, expression of both AOX 1 and ALDH is increased during oxidative or aldehyde stress (Maeda et al., 2012; Vasiliou and Nebert, 2005). This may explain the strong association of PAr with the marker of cellular immune activation, KTR, which reflects the activation of indoleamine 2,3-dioxygenase (IDO), an enzyme under redox control and with peroxidase activity (Freewan et al., 2013; Yeung et al., 2015).

The PAr index has recently been shown to be a predictor of incident cancer in the general population. The association was strongest for lung cancer (Zuo et al., 2015). Inflammation has been assigned a role in lung carcinogenesis, which is also predicted by markers of IDO activation and cellular immunity in recent prospective studies (Chuang et al., 2014; Zuo et al., 2014). In patients with angina pectoris, PAr was a stronger predictor of all-cause mortality than current smoking, diabetes, hypertension, apolipoproteins or CRP. The association with PAr was strongest in patients with no prior coronary events (Ulvik et al., 2016).

6. Mobilization of vitamin B6 during inflammation

The research reviewed above demonstrates that inflammation leads to a marked reduction in plasma PLP, and small changes in erythrocyte PLP; both plasma and erythrocyte PLP show a minor response to pyridoxine supplementation, whereas PL increases markedly. These observations suggest that depletion of PLP is confined to certain compartments, an idea supported by the results obtained in rats with adjuvant arthritis, which caused a marked reduction in PLP in liver and plasma, but not in muscle (Chiang et al., 2005). Plasma PLP probably reflects the vitamin B6 status in liver (Lumeng et al., 1980), which contains a rapidly exchanging PLP pool (Bode and van den Berg, 1991) that is mobilized via circulation to the sites of inflammation. Inflammation is associated with decreased serum albumin and increased circulating ALP (Aida, 1993; Chiang et al., 2005). These changes may facilitate mobilization of plasma PLP, by reducing PLP binding to albumin (Bates et al., 1999b; Cheng et al., 2006; Chiang et al., 2005; Huang et al., 2005; Lumeng et al., 1974; Quasim et al., 2005) and, more importantly, by increasing dephosphorylation of free PLP to PL (Narisawa et al., 2001; Vasilaki et al., 2008; Whyte et al., 1985).

Conceivably, altered vitamin B6 distribution during inflammation may not be restricted to sites of inflammation, but may also involve unaffected tissues or cells. CRP, is a marker of the IL-1β/TNF-α/IL-6 pathway (Eklund, 2009; Ridker, 2016). IL-6 upregulates ALP, required for the uptake of PLP from the circulation (Gallo et al., 1997; Kapojos et al., 2003). IL-1β and IL-6 are among the activators of the hypothalamic-pituitary-adrenal (HPA) axis where cortisol is the final key messenger (Kageyama and Suda, 2009; van der Meer et al., 1996; Venihaki et al., 2001). Cortisol has widespread effects in the body and is the main regulator of the physiological stress response including the upregulation of gluconeogenesis and degradation of protein in muscle, gut, and connective tissue. The liberated amino acids may then be utilized for energy production, synthesis of immunomodulating proteins, immune cell proliferation, and tissue repair. All of these processes require, and may therefore increase the cellular demand for PLP. Moreover, an increase in intracellular PLP has been implicated in the modulation of the cell's response to glucocorticoids (Tully et al., 1994). Glucocorticoids may have profound effects on vitamin B6 metabolism and distribution as demonstrated in mice given long-term prednisone treatment. Prednisone induced an increase in plasma PLP, PL and PA. There was a concurrent increase in the activities of PLP synthesizing enzymes (pyridoxal kinase (PDXK), pyridoxamine 5-phosphate oxidase (PMPO)) and a suppression of pyridoxal 5′-phosphate phosphatase (PDXP) in the liver whereas plasma ALP was not affected (Chang et al., 2011).

The changes in tissue vitamin B6 distribution during inflammation may modulate PLP-dependent enzymes and metabolic pathways that play a significant role in the inflammatory response. Vitamin B6-dependent networks of metabolites with immunomodulating effects and/or that respond to inflammation could be denoted as vitamin B6-dependent inflammatory pathways. Some vitamin B6-dependent inflammatory pathways that have been extensively studied in recent years are reviewed below.

7. Vitamin B6 and inflammatory pathways

7.1. The kynurenine pathway

The essential amino acid, tryptophan (Trp) is mainly catabolized along the so-called kynurenine pathway that produces a variety of compounds, collectively termed kynurenines (Fig. 2), many of which have immunomodulatory effects. Several enzymes involved in the kynurenine pathway require PLP as co-factor and their expression is regulated by inflammatory cytokines.

7.1.1. The pathway

The first and rate-limiting step in the kynurenine pathway is the oxidative cleavage of the indole ring of Trp to form N-formylkynurenine (Wang et al., 2015), which is enzymatically (by formamidase) or spontaneously decomposed to kynurenine (Kyn) and formic acid (Thomas and Stocker, 1999). The formation of N-formylkynurenine is catalyzed by three enzymes, tryptophan 2,3-dioxygenase (TDO), indolamine 2,3-dioxygenase 1 (IDO1) and IDO2 (Ball et al., 2014; Chen and Guillemin, 2009). Kyn is further metabolized to kynurenic acid (KA) or anthranilic acid (AA) through reactions catalyzed by kynurenine aminotransferases (KAT) (Han et al., 2010a; Passera et al., 2011; Pinto et al., 2014) or kynureninase (KYNU) (Phillips, 2014), respectively, both of which require PLP as co-factor. Alternatively, Kyn is oxidized to 3-hydroxykynurenine (HK) in a reaction catalyzed by the FAD-dependent enzyme, kynurenine 3-monooxygenase (KMO) (Smith et al., 2016). HK in turn is metabolized either to xanthurenic acid (XA) by KAT or 3-hydroxyanthranilic acid (HAA) by KYNU, and HK therefore occupies a unique position in the kynurenine pathway, since its further metabolism is dependent on PLP. HAA is

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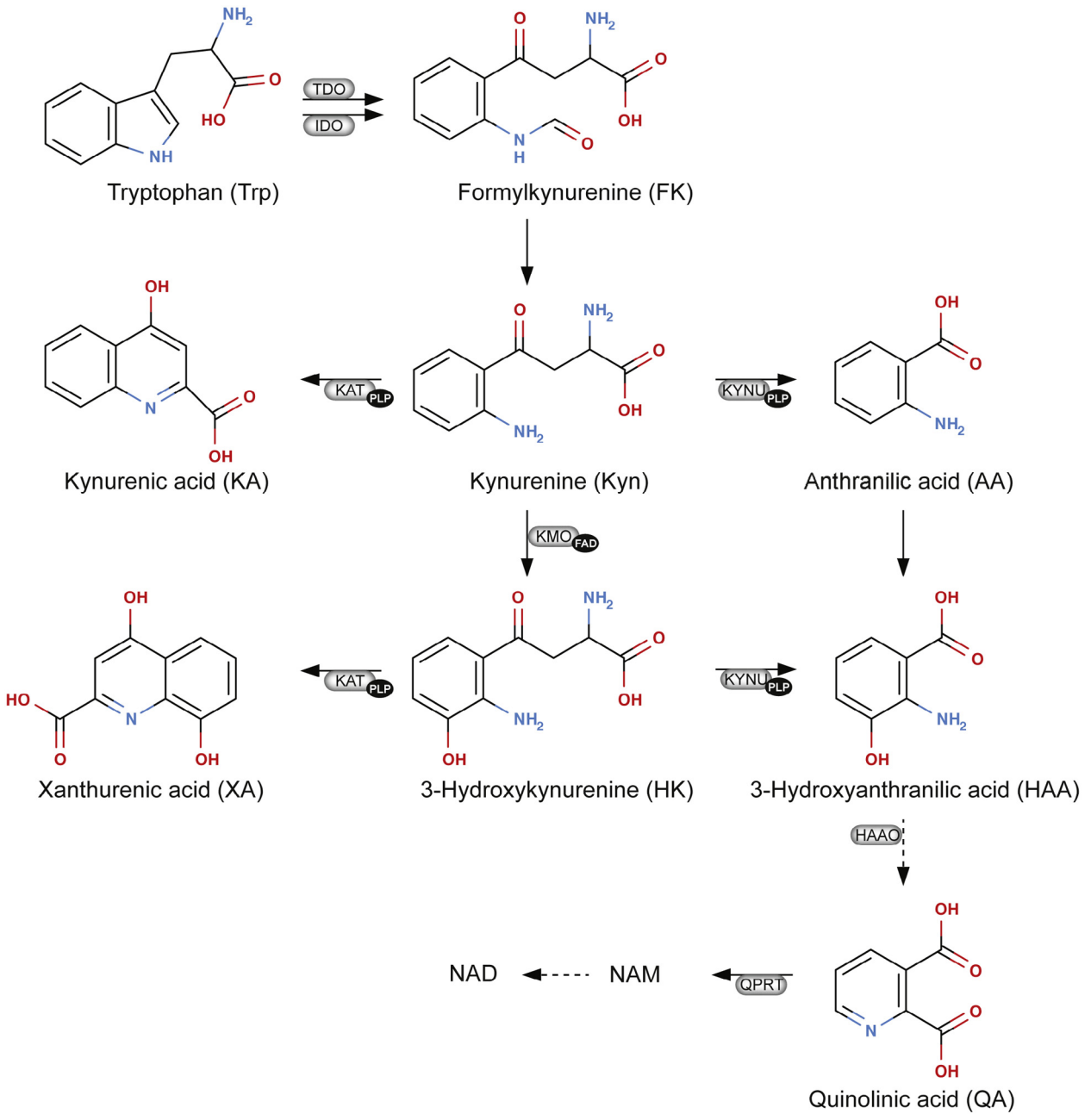

Fig. 2. Kynurenine pathway of tryptophan metabolism and the enzymes involved. The pathway includes a variety of metabolites, collectively termed kynurenines, some of which are neuroactive compounds and some have immunomodulatory effects. The first and rate-limiting step of tryptophan catabolism is the oxidation of tryptophan to N-formylkynurenine, catalyzed by the heme dioxygenases, hepatic tryptophan (2,3)-dioxygenase (TDO; EC 1.13.1.2) and ubiquitous indoleamine (2,3)-dioxygenase (IDO; EC 1.13.11.42); for the latter enzyme two gene homologues, IDO1 and IDO2, have been identified. IDO1 is activated by proinflammatory cytokines such as interferon-γ and tumor necrosis factor-α. *N*-Formylkynurenine is rapidly converted to kynurenine (Kyn), a reaction that occurs spontaneously or is catalyzed by formamidase (EC 3.5.1.9; not shown). Further metabolism of Kyn involves two pyridoxal 5′-phosphate (PLP)-dependent enzymes, kynureninase (KYNU; EC 3.7.1.3) and kynurenine aminotransferase (KAT), that catalyze the formation of anthranilic acid (AA) and kynurenic acid (KA), respectively. Alternatively, kynurenine is oxidized in a reaction catalyzed by the FAD-dependent enzyme, kynurenine 3-monooxygenase (KMO; EC 1.14.13.9), to 3-hydroxykynurenine (HK), which is further metabolized to 3-hydroxyanthranilic acid (HAA) or xanthurenic acid (XA) catalyzed by KYNU and KAT, respectively. 3-Hydroxyanthranilate 3,4-dioxygenase (HAAO); EC 1.13.11.6) converts HAA to 2-amino-3-carboxymuconate semialdehyde (ACMS), which spontaneously cyclizes to quinolinic acid (QA). QA is decarboxylated and conjugated with phosphoribosylpyrophosphate to form nicotinamide mononucleotide (NAM) in a reaction catalyzed by quinolinate phosphoribosyltransferase (QPRT; EC 2.4.2.19). Modified from Ueland et al. (2015).

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oxidized by 3-hydroxyanthranilate 3,4-dioxygenase (HAAO) (Zhang et al., 2005) into 2-amino-3-carboxymuconate semialdehyde (ACMS), which is either enzymatically converted to picolinic acid or spontaneously reassembled to form quinolinic acid (QA). In a reaction catalyzed by quinolinate phosphoribosyltransferase (QPRT), QA is subsequently converted into nicotinic acid mononucleotide (Liu et al., 2007), and ultimately NAD+ (Magni et al., 1999). NAD formation is a minor pathway in the liver, and suggested to be regulated by niacin intake (Moffett and Namboodiri, 2003).

7.1.2. Key enzymes

TDO is a heme-containing enzyme that is mainly expressed in the liver but also in some tumour cells (Opitz et al., 2011; Pilotte et al., 2012; van Baren and Van den Eynde, 2015). It is a high K_m enzyme that initiates Trp degradation (Batabyal and Yeh, 2007), is induced by corticosteroids and Trp (Salter and Pogson, 1985), and is the main enzyme responsible for catabolism of dietary Trp and maintenance of Trp homeostasis (Ball et al., 2014).

IDO1 is also a heme-containing enzyme but with a different structure, tissue distribution, regulatory and kinetic properties as compared with TDO (Yeung et al., 2015). It is expressed extra-hepatically in a variety of cells and tissues, including monocyte-derived macrophages, dendritic cells (Guillemin et al., 2001), epithelial cells, brain (Guillemin et al., 2001, 2005) and cancer cells (van Baren and Van den Eynde, 2015). Notably the morphological features of IDO1-expressing cells often resemble those of antigen presenting cells (Dai and Zhu, 2010). Compared to TDO, IDO1 shows less substrate specificity and lower K_m for Trp (Austin et al., 2009; Pantouris et al., 2014). IDO1 expression is induced by various cytokines, and among these the Th-1-type cytokine, INF-γ, is most important (Mandi and Vecsei, 2012). Thus, the ratio between Kyn and Trp (KTR) in the circulation reflects the activation of IDO and serves as a useful marker of cellular Th-1-type immune activation (Schrocksnadel et al., 2006).

IDO2 is a newly discovered paralogue to IDO1 (Murray, 2007) with a similar genomic structure (43% homology) and adjacent chromosomal localization, but with different tissue distribution and kinetic properties (Ball et al., 2007; Metz et al., 2007; Yuasa et al., 2007). IDO2 is constitutively expressed in liver, kidneys, spermatozoa and dendritic cells. It has lower V_{max}, higher K_m for Trp and shows less substrate specificity as compared with IDO1 (Ball et al., 2014; Pantouris et al., 2014; Yuasa et al., 2007). Data on its biological role are limited, but IDO2 seems to be important for the induction of several inflammatory cytokines, and may play a role in autoimmune response, immune tolerance and cancer cell surveillance (Metz et al., 2014; Prendergast et al., 2014).

Kynurenine 3-monooxygenase (KMO) is a NAD(P)H-dependent flavin monooxygenase that catalyzes the conversion of Kyn to HK (Smith et al., 2016). It is a mitochondrial enzyme that is expressed at high levels in the liver, kidney and macrophages, but also in microglia in the CNS (Alberati-Giani et al., 1997; Allegri et al., 2003; Guillemin et al., 2003). KMO has low K_m in the micromolar range, suggesting that it keeps intracellular Kyn at a low level (Breton et al., 2000). Of note, KMO expression seems to be stimulated during inflammation and immune activation (Campbell et al., 2014; Connor et al., 2008; Parrott and O'Connor, 2015).

Kynurenine aminotransferases (KATs) are PLP-dependent enzymes that exist as four different isoforms, i.e. KATI/II/III/IV. They have different tissue distribution and different substrate specificities, which is reflected by their alternate names, KATI/glutamine transaminase K/cysteine conjugate β-lyase 1, KATII/aminoadipate aminotransferase (Han et al., 2008, 2009a, 2009b), KATIII/glutamine transaminase L (Yu et al., 2006) and KATIV/mitochondrial aspartate aminotransferase (Han et al., 2010a, 2010b, 2011). KATI and KATIII have sequence homology and the highest k_{cat}/K_m values with glutamine (Han et al., 2004, 2009a, 2009b; Yu et al., 2006). KATII is the most abundant isoform in human brain and is hypothesized to be the main source of cerebral synthesis of the neuroprotective kynurenine, KA (Guidetti et al., 2007). Expression of KATI and KATIII, but not KATII, may be down regulated by the proinflammatory cytokine, IL-1β (Zunszain et al., 2012).

Kynureninase (KYNU) is a PLP-dependent enzyme that catalyzes two steps in the kynurenine pathway, i.e. the conversion of Kyn to AA and HK to HAA (Alberati-Giani et al., 1996a, 1996b; Walsh and Botting, 2002). In humans, there is expression of one KYNU (Alberati-Giani et al., 1996a, 1996b), which is mainly located in cytoplasm and has higher k_{cat}/K_m for HK than for Kyn (Alberati-Giani et al., 1996b). The formation of HAA is a key step toward the formation of NAD. Notably, KYNU is heavily upregulated during inflammation (Harden et al., 2015) and its expression is increased in murine macrophages by INF-γ (Alberati-Giani et al., 1996a) and in human keratinocytes by IL-17 and TNF-α (Chiricozzi et al., 2011). It has been suggested that KYNU serves as a switch between immunosuppression versus inflammation (Harden et al., 2015).

7.1.3. Biological effects from metabolites

Early hypotheses suggested that activation of Trp catabolism through the kynurenine pathway reduced Trp bioavailability thereby causing Trp starvation and subsequently inhibiting growth of pathogens and proliferative cells. Thus, Trp depletion was regarded as antimicrobial and antitumoral defense mechanism induced by INF-γ produced by immunocompetent cells (de la Maza and Peterson, 1988; Ozaki et al., 1988; Pfefferkorn, 1984). However, recent studies have demonstrated that Kyn is not an inert metabolic intermediate. Kyn has specific roles, such as being an endothelium-derived vasodilator produced during inflammation (Wang et al., 2010), and an endogenous ligand for the aryl hydrocarbon receptor (AhR) (Opitz et al., 2011), a ligand sensitive transcription factor that mediates (among other functions) immunosuppression (Bessede et al., 2014). Activation of AhR in turn may upregulate IDO (Bessede et al., 2014) thereby promoting the generation of regulatory T cells (Mezrich et al., 2010).

Kynurenic acid (KA), an end product of the KAT branch of the kynurenine pathway, is a neuroprotective and immunomodulating metabolite that inhibits the N-methyl-D-aspartate (NMDA) receptor and α-7-nicotine acetylcholine receptor (α-7-NAChR) in the CNS (Moroni et al., 2012). Notably, KA is an endogenous ligand of the orphan G protein-coupled receptor 35 (GPR35) (Wang et al., 2006) and AhR (DiNatale et al., 2010), which may in part mediate its immunomodulating effects. KA has also been considered as

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a potent endogenous antioxidant that scavenges hydroxyl radicals, superoxide anions and peroxynitrite (Lugo-Huitrón et al., 2011).

Anthranilic acid (AA) is generally considered a biologically inert metabolite with possible hydroxyl radical scavenging properties (Miche et al., 1997). The redox active metabolite, 3-hydroxyanthranilic acid (HAA), is a potent antioxidant (Giles et al., 2003; Leipnitz et al., 2007; Thomas et al., 1996) with anti-inflammatory and immunosuppressive effects (López et al., 2008; Weber et al., 2006) involving the induction of apoptosis in activated T-cells (Fallarino et al., 2002; Hayashi et al., 2007; Lee et al., 2010b). Possible mechanisms include increased heme oxygenase-1 (HMOX1) expression (Krause et al., 2011), inhibition of inducible nitric oxide synthase (iNOS) (Sekkaï et al., 1997), depletion of glutathione (GSH) (Lee et al., 2010b), and inhibition of 3-phosphoinositide-dependent protein kinase 1 (PDK1) phosphorylation (Hayashi et al., 2007).

3-Hydroxykynurenine (HK) is a redox active, reactive oxygen species (ROS) generating Trp metabolite (Vazquez et al., 2000) with neurotoxic effects (Smith et al., 2009). Recent studies demonstrated, however, that HK has a dual role by serving either as a prooxidant or an antioxidant (Leipnitz et al., 2007), depending on the experimental system, suggesting that HK is not neurotoxic or cytotoxic *per se*, but rather serves as a redox modulator by stimulating the redox defense system, including increasing the expression of Nuclear factor erythroid 2-related factor 2 (Nrf2) (Colín-González et al., 2014a, 2014b), the master mediator of anti-inflammatory effects (Ma, 2013).

Xanthurenic acid (XA) is formed by transamination of HK, which has been considered to represent a reaction preventing build-up of high, potentially toxic concentration of HK (Gobaille et al., 2008). XA crosses the blood–brain barrier, and may play a role in neurotransmission/neuromodulation (Gobaille et al., 2008) by activating glutamate receptor mGlu2/3 (Fazio et al., 2015). It is a metal-chelating (Murakami et al., 2006) and photochemically active (Roberts, 2001) compound with antioxidant (Christen et al., 1990) and prooxidant (Murakami et al., 2006) properties, depending on the experimental system. These properties have been related to its possible role in cataractogenesis (Roberts, 2001), lens epithelial cell apoptosis (Malina et al., 2002), and development of diabetes (Oxenkrug, 2015). Notably, XA has recently been found to be a potent inhibitor of the biosynthesis of tetrahydrobiopterin (Haruki et al., 2015), which serves as a cofactor of three aromatic amino acid hydroxylases and nitric oxide synthase (NOS).

3-Hydroxyanthranilic acid dioxygenase (HAAO) converts HAA to 2-amino 3-carboxymuconate semialdehyde (ACMS), a fraction of which is spontaneously converted to quinolinic acid (QA) (Malherbe et al., 1994). The most prominent feature of QA is its ability to serve as an endogenous NMDA-type glutaminergic receptor agonist, which explains its excitotoxicity, cytotoxic effects on neurons and astrocytes, and induction of seizures. Additional biological effects of QA include increased neuronal glutamate release, induction of oxidative stress (Colín-González et al., 2014a, 2014b; Vandresen-Filho et al., 2015), disruption of the blood–brain barrier, induction of neuronal nitric oxide synthase (*nNOS*) and *i*NOS (Braidy et al., 2009), cytoskeleton destabilization (Pierozan et al., 2014), increased tau phosphorylation (Rahman et al., 2009) and increased expression of several proinflammatory cytokines (Lugo-Huitrón et al., 2013). Human neurons do not produce significant amounts of QA, but neuronal cells take up QA produced by activated microglia and infiltrating macrophages (Guillemin, 2012). The kynurenine pathway and thereby the synthesis of QA by these cells is substantially increased during inflammation, leading to accumulation of QA, which explains the key role of QA in neuroinflammation (Guillemin, 2012).

7.1.4. Kynurenine pathway metabolites and vitamin B6 status

It has been consistently demonstrated that the concentrations of kynurenines in urine and plasma/serum are affected by vitamin B6 status in humans. Vitamin B6 deficiency caused a more than 30-fold increase in urinary excretion of XA, Kyn and HK after a tryptophan load in women. There was also a moderate increase in urinary HAA and QA (Yeh and Brown, 1977). Supplementation of subjects having adequate vitamin B6 status with PN decreased urinary excretion of XA, Kyn and HK after a tryptophan load, suggesting that PLP-dependent enzymes of the kynurenine pathway may not be fully saturated with the PLP cofactor (Leklem, 1971). The responsive metabolites, XA, Kyn and HK, precede the cleavage of HK to HAA catalyzed by KYNU, which is more sensitive than KAT to vitamin B6 depletion (Ogasawara et al., 1962; van de Kamp and Smolen, 1995). Among plasma kynurenines, only HK shows a marked increase in subjects with low plasma PLP (Theofylaktopoulou et al., 2014) and is reduced in subjects supplemented with PN (Midttun et al., 2011). Plasma KA, AA, XA and HAA show a positive relation with PLP (Theofylaktopoulou et al., 2014; Ulvik et al., 2013), while KA and HAA show a slight decrease following PN supplementation (Midttun et al., 2011). These variations in urinary and plasma kynurenines according to vitamin B6 status reflect the critical role of PLP availability for steady state metabolite concentrations and conceivably flux through the kynurenine pathway.

Urinary excretion of XA after a tryptophan load and the plasma HK/XA ratio have been established as functional markers of vitamin B6 status, as summarized in a recent review article (Ueland et al., 2015).

7.1.5. Kynurenine pathway metabolites and chronic diseases

The kynurenine pathway is upregulated under pathological conditions characterized by involvement of immune activation in pathogeneses or established disease. Such activation causes Trp depletion and formation of neuroactive kynurenines with immunomodulating effects, and has been suggested to play a role in numerous disorders, including neurodegenerative diseases (Parrott and O'Connor, 2015), depression (Meier et al., 2015; Réus et al., 2015), schizophrenia, infections, osteoporosis (Michalowska et al., 2015), rheumatoid arthritis, cancer and cardiovascular disease (Chen and Guillemin, 2009; Munn and Mellor, 2013).

In neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease and Huntington's disease, there appears to be a shift toward QA and HK synthesis, and away from KA production (Maddison and Giorgini, 2015). Multiple sclerosis relapse (Rajda et al., 2015) and schizophrenia

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(Parrott and O'Connor, 2015) have been associated with increased KA in plasma and CSF. Increased concentrations of key metabolites of the kynurenine pathway are linked to processes associated with development of cardiovascular diseases, such as immune activation, inflammation, generation of ROS, endothelial dysfunction, and vasodilation (Wang et al., 2015). Both IDO1 and less frequently TDO are expressed in human tumours, which explain increased Trp catabolism, Trp depletion and increased levels of immunomodulating kynurenines in cancer. These are mechanisms that mediate tumoral immune resistance and suppression of cancer immunosurveillance (van Baren and Van den Eynde, 2015).

Most investigations of the kynurenine pathway in relation to disease involve experimental studies in animals or cells and small clinical studies in humans. Recently, large cross-sectional and prospective studies including thousands of participants have been published. KTR (which reflects IDO activation), Kyn (Sulo et al., 2013), HK, and to a lesser extent other kynurenines (Eussen et al., 2015; Pedersen et al., 2015; Zuo et al., 2016) in plasma, and KTR in urine (Pedersen et al., 2013) are associated with risk of cardiovascular disease. Additionally, KTR is associated with risk of overall cancer, with strongest risk estimates observed for lung cancer (Chuang et al., 2014; Zuo et al., 2014), a malignancy where inflammation is believed to play a role in carcinogenesis. KTR and/or some downstream kynurenines were also associated with bone mineral density and hip fracture in a recent large cross sectional, population based study (Apalset et al., 2014a, 2014b).

7.2. Sphingolipids

The vitamin B6 antagonist, 4′-deoxypyridoxine (DOP) (Trakatellis et al., 1997), and the food colorant, 2-acetyl-4-tetrahydroxybutylimidazole (THI) (Gobin and Paine, 1989; Ohtoyo et al., 2015), have been shown to cause a reduction in circulating lymphocytes when given to rodents. These effects were fully reversible by addition of vitamin B6 (Gobin and Paine, 1989; Trakatellis et al., 1997). In 2005, the group of Jason Cyster reported that DOP and THI inhibit the enzyme, sphingosine 1-phosphate lyase (SPL), thereby causing a build-up of sphingosine 1-phosphate (S1P) in lymphoid organs, and concomitant lymphopenia, the latter reflecting inhibition of lymphocyte egress into the circulation (Schwab et al., 2005).

S1P is a bioactive sphingolipid, the *de novo* synthesis of which starts with the PLP-dependent enzyme, serine palmitoyltransferase (SPT). This is the rate limiting reaction forming 3-ketosphinganine, which is converted to ceramide (a sphingolipid) in a series of reactions (Bourquin et al., 2011). Alternatively, ceramide is formed from dietary sphingomyelin through the action of sphingomyelinase. Ceramidase (CA) catalyzes the conversion of ceramide to sphingosine, which is phosphorylated to S1P by two sphingokinases (SKs), SK1 and SK2 (Liu et al., 2012; Pyne et al., 2015). S1P can be dephosphorylated to sphingosine by two S1P-specific phosphatases, SPP1 and SPP2, or by lipid non-specific phosphatases (Liu et al., 2012). Notably, the irreversible degradation of S1P to trans-2-hexadecenal and phosphoethanolamine is catalyzed by the PLP-dependent sphingosine 1-phosphate lyase (SPL), which is an enzyme that regulates the steady state S1P concentration in tissues and the circulation (Aguilar and Saba, 2012; Bourquin et al., 2011) (Fig. 3).

S1P formed in the intracellular compartment is secreted into the extracellular environment; S1P concentration is relatively low in interstitial fluid and tissues (~nM), but high in the lymph (~0.1 μM) and the bloodstream (~1 μM), where it circulates bound to high-density lipoprotein (Blaho et al., 2015) and albumin (Książek et al., 2015; Yatomi, 2008). The biological effects of S1P appear to be mediated primarily by S1P serving as a high-affinity ligand of five specific cell-surface G-protein-coupled receptors (GPCRs), designated $S1P_{1-5}$ (Blaho and Hla, 2014). In addition, S1P activates Nuclear factor-κB (NF-κB) and Signal transducer and activator of transcription 3 (STAT3), two transcriptional regulators that serve as master switches in inflammation and carcinogenesis (Alvarez et al., 2010; Lee et al., 2010a).

The receptors $S1P_{1-5}$ mediate effects in many facets of mammalian biology, including integrity and development of the vasculature and nervous system (Blaho and Hla, 2014; Proia and Hla, 2015). Activation of the $S1P_1$ is critical for the egress of lymphocytes residing in the secondary lymphoid organs and thymus (Chi, 2011; Cyster and Schwab, 2012; Proia and Hla, 2015) and is involved in regulating differentiation of T-cells, including T helper 17 (Garris et al., 2013) and T helper 1/regulatory T cell balance (Liu et al., 2010).

Ceramide is formed *de novo* as an intermediate during synthesis of S1P. The PLP-dependent enzyme, SPT, which links ceramide to vitamin B6 function, catalyzes the first step. Enzymes involved in other routes of ceramide synthesis or degradation are not vitamin B6-dependent. Ceramide kinase (CK) converts ceramide to ceramide 1-phosphate (C1P) (Fig. 3). Ceramide and C1P have been liked to inflammation, but data are less compelling than for S1P, and a surface receptor for C1P is yet to be validated. (Maceyka and Spiegel, 2014).

C1P activates cytosolic phospholipase–A2α and thereby synthesis of arachidonate for the production of eicosanoids. C1P also plays a role in the processing of the proinflammatory cytokine TNF-α. Other functions of C1P include promoting cellular proliferation and growth, macrophage migration, and inhibition of apoptosis (Gomez-Muñoz et al., 2015).

7.3. Transsulfuration pathway and hydrogen sulfide formation

The gaseous messenger *hydrogen sulfide* (H_2S) has emerged as a regulator of inflammatory response. H_2S has antiinflammatory effects at low, physiological concentrations, but is proinflammatory at high concentrations (Bhatia, 2012; Gemici and Wallace, 2015; Whiteman and Winyard, 2011). H_2S also serves as a regulator of numerous other physiological functions, including vasodilation, angiogenesis (Liu et al., 2011), neurotransmission, apoptosis and insulin release (Bełtowski, 2015; Paul and Snyder, 2012). Cysteine is the major thiol in plasma, and the redox state of cysteine/cystine may itself play a role in inflammatory signaling (Go and Jones, 2011). It also serves as a key component in GSH synthesis (Stipanuk and Ueki, 2011). GSH is not only an

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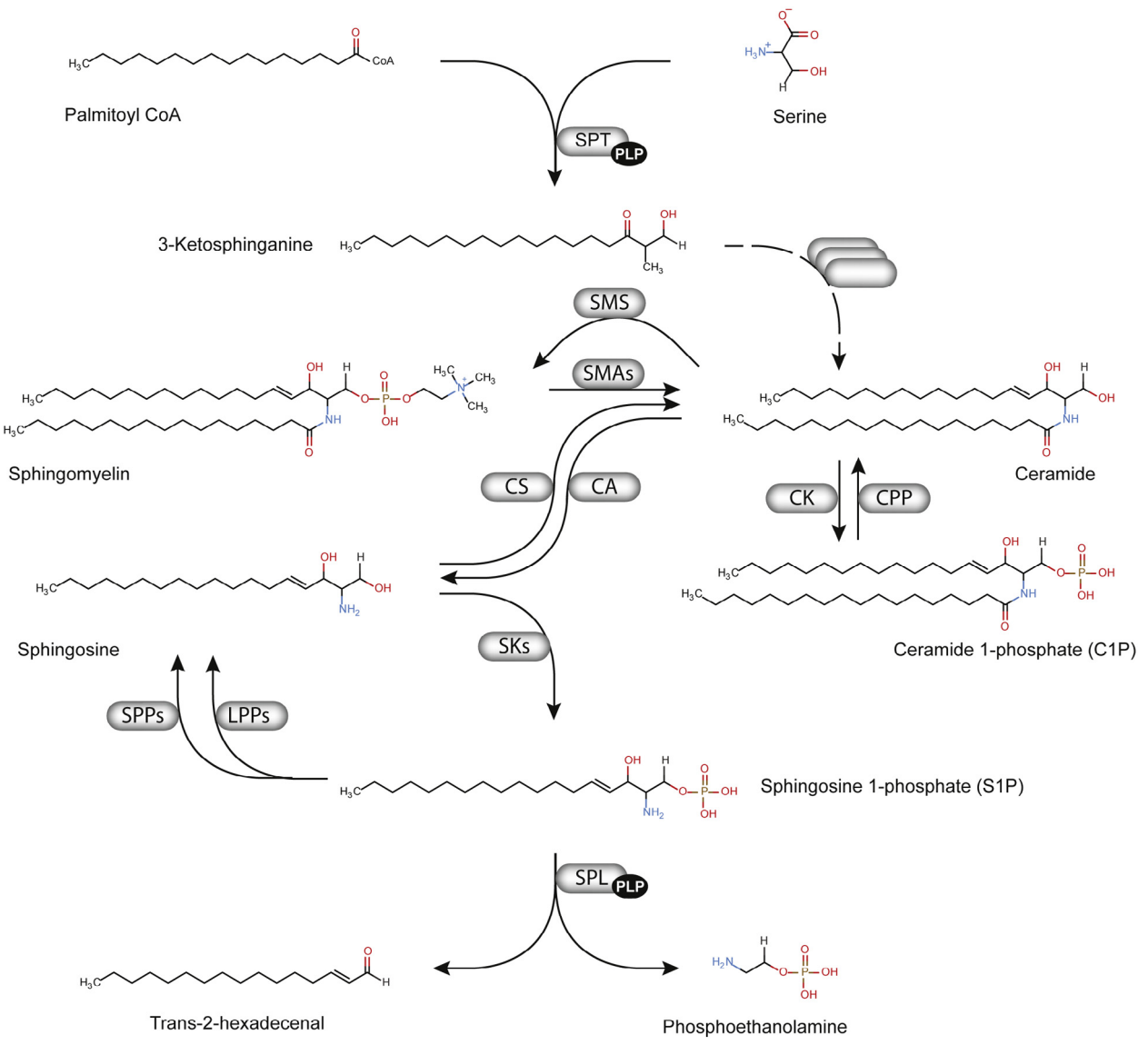

Fig. 3. Metabolism of sphingolipids and the enzymes involved. Sphingolipids are synthesized *de novo* in the endoplasmic reticulum and synthesis is initiated by the condensation of L-serine with palmitoyl-CoA catalyzed by the PLP-dependent enzyme serine palmitoyltransferase (SPT; EC 2.3.1.50) forming 3-ketosphinganine, which is metabolized to ceramide through three enzymatic steps. Newly synthesized ceramide is transported to the Golgi apparatus where it is converted to sphingomyelin in a reaction catalyzed by sphingomyelin synthase (SMS; EC 2.7.8.27). Degradation in the lysosomes and plasma membrane of higher-order sphingolipids leads to the formation of ceramide, which is converted to sphingosine in a reaction catalyzed by ceramidase (CA; EC 3.5.1.23). Sphingosine kinase(s) (SKs; EC 2.7.1.91) catalyzes the conversion of sphinogosine to sphinogosine 1-phosphate (S1P) in multiple compartments. S1P can be dephosphorylated to sphinogosine by enzymes like the ecto enzymes, lipid non-specific phosphatases (LPP1, LPP2 and LPP3), and by S1P-specific phosphatases (SPP1 and SPP2; EC 3.1.3.-), localized in the plasma membrane and endoplasmic reticulum, respectively. Notably S1P is irreversibly degraded in endoplasmic reticulum by PLP-dependent enzyme S1P lyase (SPL; EC 4.1.2.27), which is the key regulator of the steady state S1P concentration in tissues and the circulation. Abbreviations: SMAs, sphingomyelinase(s); CS, Ceramide synthase; CK, Ceramide kinase; CPP, Ceramide 1-phospahte phosphatase.

antioxidant, detoxifying reactive oxygen species, but also a signaling molecule that regulates innate immunity and inflammation (Ghezzi, 2011), effects partly mediated by cytokines and redox-sensitive transcription factors like NF-κB and Hypoxia-inducible factor-1α (HIF-1α) (Haddad and Harb, 2005).

The formation of H_2S and cysteine involves two PLP-dependent enzymes, cystathionine β-synthase (CBS) (Miles and Kraus, 2004) and cystathionine γ-lyase (CSE) (Kraus et al., 2009). The sequential action of these two enzymes comprises the transsulfuration pathway responsible for the conversion of homocysteine to cysteine through the intermediate, cystathionine (Stipanuk and Ueki, 2011) (Fig. 4). About 20–50% of cysteine used for GSH synthesis in the liver is derived from the transsulfuration pathway (Gregory et al., 2016; Mosharov et al., 2000), which seems to be responsible for the bulk of H_2S generated for regulatory purposes (Kabil and Banerjee, 2014).

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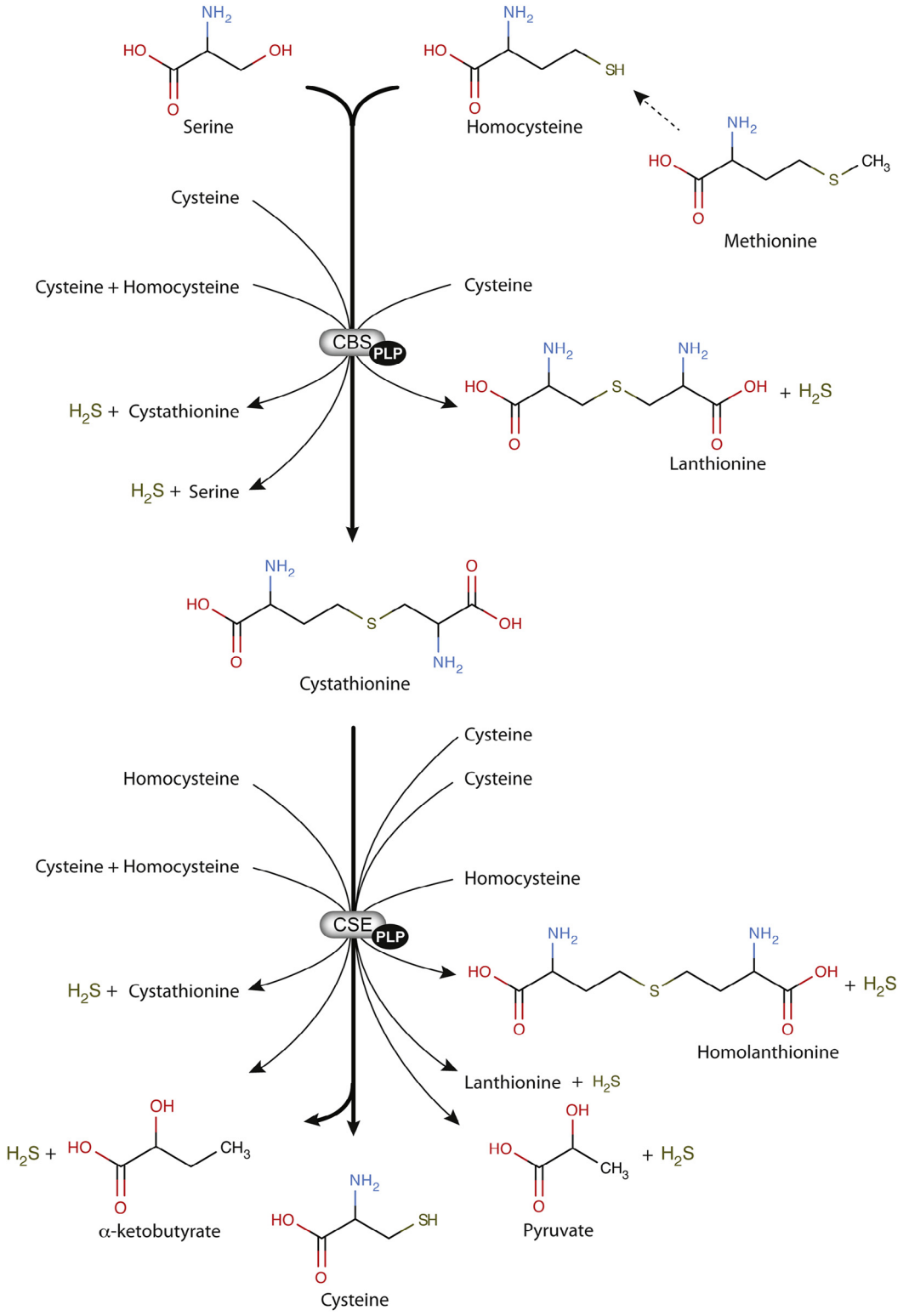

Fig. 4. The transsulfuration pathway, H_2S production and the enzymes involved. Methionine is activated to the universal methyl donor, S-adenosylmethionine, which is converted to S-adenosylhomocysteine during S-adenosylmethionine-dependent transmethylation reactions. S-adenosylhomocysteine in turn is hydrolyzed to adenosine and homocysteine in a reaction catalyzed by S-adenosylhomocysteine hydrolase (not shown). Homocysteine is either remethylated to methionine (not shown) or converted to cysteine via the transsulfuration pathway, where homocysteine is converted to cysteine through the sequential action of two PLP-dependent enzymes, cystathionine β-synthase (CBS; EC 4.2.1.22) and cystathionine γ-lyase (CSE; EC 4.4.1.1). H_2S is produced through seven non-canonical reactions catalyzed by CBS and CSE, as indicated.

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Both CBS and CSE are ubiquitous, but CBS is expressed predominately in the brain and kidney while CSE is expressed primarily in the peripheral tissues like liver and cardiovascular tissue. In the first step in the transsulfuration pathway CBS catalyses the synthesis of cystathionine by condensing homocysteine with serine. H_2S is formed during non-canonical reactions catalyzed by CBS. These reactions include cysteine desulfuration by linking homocysteine with cysteine (instead of serine) (Chen et al., 2004), and conversions of cysteine to serine or lanthionine (Stipanuk and Ueki, 2011).

CBS has a catalytic domain that binds PLP and resembles the catalytic core of other members of fold II family of PLP-dependent enzymes. It has two regulatory domains at the N- and C-terminals, respectively. The N-terminal heme domain serves as a redox gas sensor mediating increased CBS activity under oxidizing conditions. Interaction of carbon monoxide (CO) and nitric oxide (NO) with the ferrous (Fe++) form of this regulatory site reduces enzyme activity whereas air oxidation leads to recovery of enzyme activity; thus CBS serves as a point of cross-talk between modulators of inflammation, like CO, NO and H_2S. The C-terminal regulatory domain inhibits enzyme activity of the full-length enzyme, and the inhibition is relieved by interaction of S-adenosylmethionine (SAM) with an allosteric site. SAM thereby coordinates the balance between methylation and redox-balance (Kabil and Banerjee, 2014).

CSE catalyzes the second step in the transsulfuration pathway where cystathionine is cleaved to cysteine and α-ketobutyrate. H_2S production results from side reactions of CSE with cysteine, homocysteine or both as substrates (Zhao et al., 2014) (Fig. 4).

CSE appears to be more inducible than CBS (Zhao et al., 2014). Numerous compounds affect H_2S production and/or regulate CSE at the transcriptional, post-transcriptional and/or post-translational levels. These include inflammation mediated by TNF-α, the transcription factors Specificity protein-1 (Sp1), oxidative stress, microRNAs (miR-21 and miR-30), testosterone, estrogens, dexamethasone, phenylephrine, insulin, glucose, NO, CO, and calcium-calmodulin (Zhao et al., 2014). Notably, calcium may interact with PLP to regulate CSE activity, and H_2S production at low calcium levels greatly depends on PLP (Mikami et al., 2013).

PLP serves as a cofactor for both CBS and CSE in the side reactions producing H_2S (Gregory et al., 2016). Kinetic simulations suggest that CBS accounts for up to 70% of transsulfuration derived H_2S formation, and the condensation of homocysteine and cysteine seems to create more H_2S than condensation of two molecules of cysteine (Singh et al., 2009). The CSE-catalyzed condensation of two homocysteine molecules may be less efficient under normal conditions, but may increase during hyperhomocysteinemia. Since CSE is more sensitive than CBS to available PLP, it has been suggested CSE-catalyzed formation of H_2S is most extensively affected by vitamin B6 status (Gregory et al., 2016).

The transsulfuration pathway is influenced by vitamin B6 status as demonstrated by increased plasma cystathionine in humans (da Silva et al., 2013; Davis et al., 2006; Lamers, 2011; Midttun et al., 2007) and rats (Stabler et al., 1997) during moderate vitamin B6 deficiency. In rats there is a concurrent increase in cystathionine in liver and muscle (Lima et al., 2006; Swendseid et al., 1964). Studies with isolated cells demonstrated higher cystathionine when cultured at moderate vitamin B6 deficiency than at severe deficiency (da Silva et al., 2014). CBS and CSE have similar affinities for PLP (Gregory et al., 2016); therefore build-up of cystathionine has been explained by higher rate of turnover for CSE than for CBS and by loss of CSE apoenzyme at low PLP (Lima et al., 2006). Build-up of cystathionine during vitamin B6 deficiency may actually maintain cysteine flux, which in turn provides sufficient cysteine to prevent a decline in GSH (Davis et al., 2006; Lima et al., 2006). This explains why vitamin B6-dependent changes in transsulfuration do not decrease GSH content in the liver during mild- to moderate vitamin B6 deficiency (Lima et al., 2006). On the contrary, dietary vitamin B6 restriction causes elevation of GSH in human plasma (Davis et al., 2006) and rat liver (Lima et al., 2006). This apparent paradox has been explained by a GSH response to oxidative stress induced by vitamin B6 restriction (Nijhout et al., 2009).

Studies with isolated cells demonstrated impaired synthesis of H_2S and the H_2S biomarkers, homolanthionine and lanthionine, during vitamin B6 restriction (DeRatt et al., 2014). However, for unknown reasons, moderate, short-term vitamin B6 insufficiency did not affect plasma concentrations of homolanthionine and lanthionine in healthy subjects (DeRatt et al., 2016).

The mechanisms whereby the products of the transsulfuration enzymes, H_2S and cysteine, modulate inflammatory response are complex (Whiteman and Winyard, 2011). Recently, there has been a focus on H_2S signaling by sulfhydration (persulfidation), which involves modification of cysteine group of numerous target proteins by conversion of a –SH group to a more reactive –SSH group (Paul and Snyder, 2015). H_2S may modulate inflammatory responses through sulfhydration of the transcription factor, NF-κB and sulfhydration of a protein that sequesters Nrf2 (Paul and Snyder, 2015).

7.4. Serine and glycine

The biosynthesis and metabolism of serine and glycine are closely linked, and they provide precursors for the synthesis of proteins, nucleic acids and lipids, which are required for the proliferation of immune cells (de Koning et al., 2003; Wang et al., 2013). Serine is a component in the synthesis of the lipid mediator, S1P (Bourquin et al., 2011), whereas glycine is involved in the synthesis of GSH (Stipanuk and Ueki, 2011). In addition, the role of glycine as an immune modulator with anti-inflammatory effects (Wheeler et al., 1999; Zhong et al., 2003) has been consistently demonstrated in isolated cells (Blancas-Flores et al., 2012; Garcia-Macedo et al., 2008), experimental animals (Alarcon-Aguilar et al., 2008; Almanza-Perez et al., 2010; Gundersen et al., 2007; Takahashi et al., 2008; Vieira et al., 2015), and in humans (Cruz et al., 2008; Zhong et al., 2003). Suggested mechanisms include activation of the non-neuronal glycine-gated chloride channel (Froh et al., 2002; Wheeler et al., 1999), reduction of TNF-α and IL-1β (Hartog et al., 2007), and increased levels of the anti-inflammatory cytokine, IL-10 (Bruck et al., 2003).

Both serine and glycine in plasma have high within-subjects reproducibility over time (Cope et al., 2013; Midttun

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et al., 2014). This observation of high individuality suggests that plasma concentrations are tightly regulated, but also ensures reliable estimates of biomarker status over time from single point measurements in epidemiological and clinical studies. Studies in humans have demonstrated that high glycine is associated with low risk of cardiovascular disease (Ding et al., 2015), type 2 diabetes (Floegel et al., 2013; Klein and Shearer, 2016), impaired insulin sensitivity and low β-cell secretory capacity (Palmer et al., 2015), observations that are in agreement with its role as an antiinflammatory agent.

The mitochondrial glycine cleavage system (GCS) and cytoplasmic and mitochondrial serine hydroxymethyltransferase (cSHMT and mSHMT) are PLP-dependent enzymes involved in serine and glycine metabolism (Scheer et al., 2005; Tibbetts and Appling, 2010) (Fig. 5). GCS catalyzes the decarboxylation of glycine to CO_2 and NH_3, whereas SHMT is responsible for the interconversion of serine and glycine; both reactions are linked to the formation of methylenetetrahydrofolate that provides activated C1-units for the synthesis of purines, thymidylate and methionine. Serine and glycine are quantitatively the most important C1-donors in humans (Appling, 1991; Tibbetts and Appling, 2010).

Serine and glycine metabolism is influenced by vitamin B6 status, as demonstrated by studies in human (Lamers et al., 2009), experimental animals (Scheer et al., 2005) and isolated cells (da Silva et al., 2014). In humans, plasma glycine and serine were increased after one to two weeks of vitamin B6 depletion; both glycine and serine were normalized after PN supplementation (Park and Linkswiler, 1971). Stable isotope flux studies in humans have demonstrated increased plasma glycine and to a lesser extent serine after 28-day controlled vitamin B6 restriction resulting in moderate vitamin B6 deficiency (da Silva et al., 2013; Davis et al., 2005; Lamers et al., 2009; Nijhout et al., 2009). Concentrations of glycine in plasma, muscle (Swendseid et al., 1964), and liver (Runyan and Gershoff, 1969; Scheer et al., 2005) were increased in rats fed a vitamin B6-deficient diet, and in HepG2 cells cultured in a medium with low vitamin B6 (da Silva et al., 2014).

Low SHMT in rat liver has been reported during vitamin B6 deficiency (Martinez et al., 2000), but results from mathematical modeling suggest that reduced glycine decarboxylase is the main cause of glycine accumulation (Lamers et al., 2009; Nijhout et al., 2009), which in turn results in more glycine being converted to excess serine by SHMT (Nijhout et al., 2009). Notably, the decarboxylase flux appears to be only slightly reduced during moderate vitamin B6 deficiency, which has been explained by maintained flux through elevated glycine concentration and a high K_m for glycine of the decarboxylase reaction (Fujiwara and Motokawa, 1983; Lamers et al., 2009; Nijhout et al., 2009).

8. Conclusion

Published results demonstrate that inflammation, immunoactivation and related diseases are associated with up to 50% reduction in plasma PLP, and minor changes in erythrocyte PLP and functional vitamin B6 biomarkers. Low plasma PLP parallels reduction in liver PLP, whereas vitamin B6 in muscle is not affected. Vitamin B6 intake or supplementation improves some immunological parameters in vitamin B6-deficient animals and humans. The available

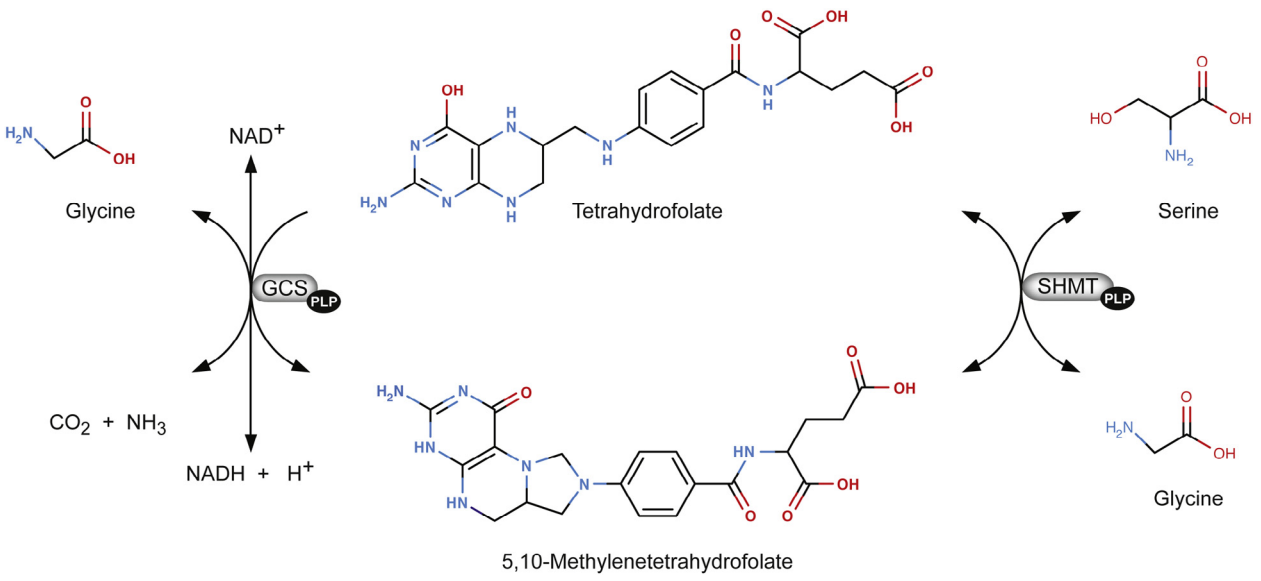

Fig. 5. Serine hydroxymethyltransferase (SHMT) and the glycine cleavage system (GCS). SHMT (EC 2.2.2.1) is a PLP–dependent enzyme that catalyzes the reversible conversions of serine to glycine and tetrahydrofolate to 5,10-methylenetetrahydofolate. In mammals there are two isoforms, a cytoplasmic (cSHMT) and a mitochondrial (mSHMT) form. GCS is also called glycine decarboxylase complex or, when run in the reverse direction, glycine synthase. GCS is a mitochondrial multienzyme system that is composed of four individual proteins, three specific components (P-, T-, and H-proteins), and one housekeeping enzyme, dihydrolipoamide dehydrogenase (L-protein). P-protein is a PLP-dependent glycine decarboxylase (glycine:lipoylprotein oxidoreductase; EC 1.4.4.2). This system is triggered by high glycine and catalyzes the oxidative cleavage of glycine. When coupled to SHMT, the overall reaction becomes: 2 glycine + NAD^+ + H_2O --> serine + CO_2 + NH_3 + NADH + H^+. Modified from Ueland et al. (2015).

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results demonstrate that inflammatory conditions are linked to a tissue-specific alteration in vitamin B6 distribution. These changes may reflect mobilization of vitamin B6 to the site of inflammation, but existing human or experimental data cannot distinguish between inflammation inducing localized vitamin B6 deficiency and deficiency promoting inflammatory processes; both mechanisms may actually be involved. Recent research aiming to delineate the mechanisms involved has focused on vitamin B6-dependent inflammatory pathways. These include vitamin B6 catabolism, the kynurenine pathway, the transsulfuration pathway, and serine and glycine metabolism. Notably, for these pathways, components in human plasma have been identified that respond to change in vitamin B6 status, demonstrating that vitamin B6 status affects steady state concentration and/or metabolic flux. The role of S1P in immune regulation and PLP-dependent SPL as a determinant of S1P concentrations in tissues and circulation have been properly documented, but there are no data demonstrating that S1P levels vary according to vitamin B6 status. Future research should seek to identify additional vitamin B6-dependent inflammatory pathways and related metabolites that mediate potential effects of variable vitamin B6 status on immune function and inflammation. Untargeted metabolomics may reveal vitamin B6 responsive metabolites, but carries the inherent weakness of detecting only abundant metabolites. Targeted metabolite profiling is a challenging task since PLP is involved in about 150 enzyme reactions.

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