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Pathogenesis of cognitive dysfunction in phenylketonuria: Review of hypotheses ☆

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ABSTRACT

In untreated phenylketonuria (PKU), deficiency of phenylalanine hydroxylase (PAH) results in elevated blood phenylalanine (Phe) concentrations and severe mental retardation. Current dietary treatment prevents mental retardation, but cognitive outcome remains suboptimal. The mechanisms by which elevated blood Phe concentrations disturb cerebral metabolism and cognitive function have not been fully elucidated.

In this review, we discuss different hypotheses on the pathogenesis of PKU, focusing on the effects of disturbed large neutral amino acid (LNAA) transport from blood to brain on cerebral neurotransmitter and protein synthesis. Although the definitive roles of these processes in PKU pathogenesis are not fully understood yet, both substantially influence clinical outcome.

Introduction

The inborn error of amino acid metabolism which characterizes phenylketonuria (PKU; OMIM 261600 and 261630)[1] is caused by mutations in the gene encoding phenylalanine hydroxylase (PAH; EC 1.14.16.1), resulting in PAH deficiency. PAH is primarily expressed in the liver and hydroxylates phenylalanine (Phe) to tyrosine (Tyr). In PKU, this hydroxylation process is disrupted. Untreated PKU is mainly characterized by elevated blood Phe concentrations, low-to-normal blood Tyr concentrations, and severe mental retardation (intelligence quotient (IQ) 30–50). Moreover, other neurological symptoms such as developmental delay, epilepsy, and behavioural problems may occur [1], as well as depression and anxiety disorders [2].

Treatment consists of restricting Phe intake by regulating intake of natural protein, combined with amino acid mixtures supplemented with trace elements to prevent nutritional deficiencies. Most experts currently advise that this treatment be continued for life. When the disorder is diagnosed and treated continuously from an early age (i.e., within the first weeks of life), mental retardation can be prevented. However, cognitive outcome is still abnormal. In early- and continuously treated PKU patients, IQ is several points lower than in healthy controls [3–5], and neurophysiological and neuropsychological impairments persist [6–10].

Despite several decades of research in PKU patients, in pharmacologically induced hyperphenylalaninemic rat and mouse models, and in the more recently developed Pah^{enu2} mouse model, the pathophysiologic mechanism by which PKU results in cognitive dysfunction remains unclear. Theoretically, cognitive dysfunction in PKU may be related to elevated blood Phe concentrations and/or reduced blood Tyr concentrations. Blood Tyr concentrations do not correlate with cognitive outcome in PKU, and Tyr supplementation alone does not prevent severe mental retardation [11]. In contrast, the relationship between cognitive outcome and blood Phe concentrations is well established. Elevated blood Phe concentrations have been shown to increase brain Phe concentrations, which are generally considered neurotoxic.

In this review, we will first discuss the effects of hyperphenylalaninemia (HPA) on large neutral amino acid (LNAA) transport from blood to brain. Next, we will address the consequences of disturbed blood-to-brain LNAA transport in HPA on cerebral neurotransmitter and protein synthesis.

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[1] *Abbreviations used:* Phe, phenylalanine; PKU, phenylketonuria; PAH, phenylalanine hydroxylase; LNAA, large neutral amino acid; Tyr, tyrosine; IQ, intelligence quotient; HPA, hyperphenylalaninemia; BBB, blood–brain barrier; LAT1-transporter, large neutral amino acid type 1 (LAT1)-transporter; EEG, electroencephalography; EAA, essential amino acid; HMGR, 3-hydroxy-3-methylglutaryl coenzyme A reductase.

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LNAA transport across the blood–brain barrier

There are two reasons why amino acid transport across the blood–brain barrier (BBB) is considered to be important in the pathogenesis of PKU. First, PKU symptomatology almost exclusively concerns the brain [1]. Second, individuals with untreated PKU have been described as having the biochemical characteristics of untreated PKU, but with normal intelligence [12–14]. Thus, it seems amino acid transport across the BBB is important in mediating the effects of elevated blood Phe concentrations on cerebral metabolism.

Amino acid transport from blood to brain is a dynamic process, facilitated by nine amino acid transporters [15], each binding to a more or less specific set of amino acids. One of these transporters is the large neutral amino acid type 1 (LAT1)-transporter, which selectively binds to the LNAAs (valine, isoleucine, leucine, methionine, threonine, tryptophan, Tyr, histidine, and Phe) [15,16]. Binding of LNAA to the LAT1-transporter is a competitive process [15–17]. Moreover, the LAT1-transporter is a counter-transporter, excreting one LNAA for each LNAA taken into the brain [18].

At physiological LNAA concentrations, the LAT1-transporter is almost fully saturated [15–17]. The LAT1-transporter has different affinities and k_m-values (the k_m-value is the substrate concentration at which the reaction rate is 50% of its maximum value) for each LNAA, and Phe has the lowest k_m-value, indicating that it binds the LAT1-transporter more strongly than other LNAA [15,16,18]. Therefore, elevated blood Phe concentrations in PKU are believed to markedly increase uptake of Phe from blood to brain and to reduce uptake of non-Phe LNAA by two mechanisms. First, non-Phe LNAA uptake into the brain is reduced because of competitive inhibition by Phe. Second, non-Phe LNAA export from the brain in exchange for blood Phe is increased. This process likely continues until a new equilibrium is reached and Phe is continually transported across the BBB, resulting in a net Phe flux of zero. In accordance with this theory, Landvogt et al. [19] reported reduced uptake of F-dihydroxyphenylalanine (F-DOPA) in PKU patients compared to healthy controls. Like LNAA, F-DOPA uptake from blood to brain is mediated by the LAT1-transporter [19]. In addition, in healthy volunteers consuming a single dose of 100 mg Phe/kg of body weight, uptake of the artificial LNAA 11-C-aminocyclohexanecarboxylate was reduced in the presence of markedly elevated plasma Phe concentrations [20].

If elevated plasma Phe concentrations disturb amino acids uptake from blood to brain, one would expect elevated brain Phe concentrations and reduced brain non-Phe LNAA concentrations in PKU. Indeed, elevated brain Phe concentrations have been described in PKU patients [8,21–24] and in the BTBR Pah^{enu2} PKU mouse model [25–30]. Moreover, reduced brain concentrations of valine, isoleucine, leucine, methionine, and Tyr have been reported in the BTBR Pah^{enu2} PKU mouse model [25,26,29]. In PKU patients, reduced brain concentrations of Tyr and tryptophan have been reported in autopsied brains [30]. It is not yet technically feasible to measure non-Phe brain LNAA concentrations non-invasively *in vivo*.

In this regard, it is important to consider that the LAT1-transporter has a saturation percentage >95% at physiological plasma LNAA concentrations [25], and that at relatively mild supraphysiological plasma Phe concentrations of 200–500 μmol/L, transport of tryptophan across the BBB is reduced, as is cerebral protein synthesis [16]. Thus, even in early- and continuously-treated patients with blood Phe concentrations within the currently recommended treatment range, LNAA transport across the BBB may be disrupted.

Based on the concept that disturbed LNAA transport is central in PKU pathogenesis, studies using oral LNAA supplementation as a PKU treatment were conducted. These studies showed that oral LNAA supplementation lowered brain Phe concentrations [21–23], mitigated electroencephalography (EEG) abnormalities [21], and improved neuropsychological performance [8].

In healthy individuals, all LNAA except Tyr are essential amino acids (EAA; i.e., they cannot be biosynthesized in man). In PKU, Tyr synthesis is reduced such that Tyr essentially functions as an EAA as well. Therefore, in untreated PKU, all LNAA are EAAs. Reduced non-Phe LNAA transport across the BBB in PKU may thus result in cerebral EAA deficiencies, possibly impairing cerebral neurotransmitter and/or protein synthesis, leading to the mental retardation and other cognitive and neurological abnormalities observed in PKU. Thus, reduced brain non-Phe LNAA concentrations, rather than elevated brain Phe concentrations, might be considered of paramount importance in the pathogenesis of PKU [31]. This theory will be discussed in more detail below.

Neurochemical findings in PKU

In the Pah^{enu2} PKU mouse model, dopamine, catecholamine, and serotonin concentrations are reduced in homogenized brain [26,29,36] and in different brain regions, including the prefrontal cortex [36–38], amygdala, hippocampus, and striatum [37–39]. Embury et al. [39,40] also reported reductions in dopaminergic cell body density in the substantia nigra and nigrostriatum, a finding possibly consistent with decreased dopamine synthesis. In PKU patients, reduced concentrations of dopamine, catecholamines, serotonin, and their metabolites have been reported that are similar to those reported in the PKU mouse brain [26,37], both in brain tissue [30] and in cerebrospinal fluid [32–34]. Dietary treatment restores neurotransmitter metabolite concentrations in the cerebrospinal fluid [32,34], as do Tyr and tryptophan supplementation [35]. Taken together, these findings suggest that reduced neurotransmitter concentrations in PKU are caused by reduced neurotransmitter synthesis rather than increased neurotransmitter degradation.

Synthesis of dopamine and catecholamines occurs via hydroxylation of Tyr to L-dihydroxyphenylalanine (L-DOPA) by tyrosine hydroxylase. L-DOPA is subsequently converted to dopamine, which is next metabolized to noradrenalin and adrenalin. Reduced synthesis of dopamine and catecholamines in PKU may be caused by competition between brain Phe and Tyr for hydroxylation by tyrosine hydroxylase [29,37,38]. Another explanation for reduced brain dopamine and catecholamine synthesis in PKU is reduced synthesis of tyrosine hydroxylase, which has been reported in the Pah^{enu2} PKU mouse model [38,39]. Alternatively, reduced brain concentrations of dopamine and catecholamines may be caused by reduced BBB transport of Tyr. This theory is supported by the reduced brain Tyr concentrations reported in PKU mice [25,29,38] and reduced brain Tyr concentrations in PKU patients [30].

Synthesis of serotonin occurs via hydroxylation of tryptophan to 5-hydroxy-tryptophan by tryptophan hydroxylase. Subsequently, 5-hydroxytryptophan is converted to serotonin (5-hydroxytryptamine). Little is known about the cause of reduced brain serotonin synthesis in PKU. Reduced serotonin synthesis may be the result of reduced tryptophan brain concentrations caused by reduced BBB transport of tryptophan at elevated plasma Phe concentrations [31]. Although brain tryptophan concentrations of PKU mice are comparable to those found in heterozygous or wild-type controls [26,29,36], reduced brain tryptophan concentrations have identified in PKU patients [30]. Alternatively, reduced brain serotonin synthesis may be caused by reduced tryptophan hydroxylase activity at elevated brain Phe concentrations. In accordance with this idea, Pascucci et al. [36] reported reduced hydroxylation of tryptophan to 5-hydroxytryptophan in PKU mice compared to controls when the amount of tryptophan hydroxylase was unaltered, suggesting reduced tryptophan hydroxylase activity. Interestingly, tryptophan hydroxylase activity was restored

after treatment with Phe-restriction without amino acid supplements [36]. This *in vivo* work supports the *in vitro* finding of an inhibitory effect of Phe on tryptophan hydroxylase activity [41].

The clinical significance of reduced brain dopamine, catecholamines, and serotonin concentrations in PKU patients has not been fully elucidated. Of these neurotransmitters, dopamine has been studied most extensively. Reduced dopamine availability may be particularly problematic for prefrontal neurons, which have a higher dopamine turnover than neurons elsewhere in the brain [3,42,43]. Dopamine availability in the dorsolateral prefrontal cortex is important in executive functioning, and thus may explain the reduced neuropsychological performance observed in PKU patients [3,6,7]. Moreover, untreated PKU patients may occasionally develop chorea, tremors, and dystonia [44,45], symptoms possibly caused by dopamine deficiency in the basal ganglia. Cerebral serotonin deficiency may explain the increased occurrence of anxiety and depression disorders in PKU patients [2,3].

Most importantly however, although both dopamine and serotonin are likely to be involved in postnatal brain development and maturation, severe mental retardation is not the most characteristic feature of inborn deficiencies of these neurotransmitters in humans [46]. Therefore, cerebral neurotransmitter deficiencies do not seem to fully explain the clinical presentation of PKU, but are likely to explain certain cognitive deficiencies.

Cerebral protein synthesis in PKU

Reduced brain non-Phe LNAA concentrations rather than elevated brain Phe concentrations may be hypothesized to be the main pathophysiologic mechanism of cognitive dysfunction in PKU. Several authors have examined reductions in cerebral protein synthesis in PKU animal models. Increases in inactive monoribosomes, reductions in polyribosomes, and reductions in polypeptide elongation have been reported in pharmacologically induced chronic HPA in mice [47,48] and after a single Phe injection [49]. In the hyperphenylalaninemic mouse brain, elevated brain Phe concentrations and reduced brain non-Phe LNAA concentrations have been reported [47,48]. LNAA supplementation restored polyribosome formation and polypeptide elongation either partially [49] or completely [47,48] and restored brain LNAA concentrations [48]. Interestingly, brain Phe concentrations were unaltered, suggesting that cerebral protein synthesis may be more affected by reduced brain non-Phe LNAA concentrations than by elevated brain Phe concentrations [48,49].

In hyperphenylalaninemic rats, reduced incorporation of ^{3}H-leucine and ^{3}H-lysine into cerebral proteins has been reported [16,50]. Reduced incorporation of ^{3}H-leucine was found to occur at plasma Phe concentrations of 200 μmol/L and higher [16]. Likewise, reduced incorporation of 14-C-leucine has been reported in the Pah^{enu2} PKU mouse model [25]. A recent study demonstrated reduced cerebral protein synthesis in early-treated PKU patients *in vivo* by PET-scanning using 1-^{11}C-tyrosine [51]. These data support the important point that cerebral protein synthesis is reduced in PKU, both in patients and in animals.

Reduced cerebral protein synthesis in PKU might explain the white matter abnormalities reported in PKU patients, in the Pah^{enu2} PKU mouse model, and in the pharmacologically induced HPA rat model. Bauman and Kemper [52] reported reduced myelination and reduced dendritic arborization of brain structures in three adults with untreated PKU at post-mortem investigation, a possible consequence of reduced cerebral protein synthesis. Moreover, abnormalities of periventricular and subcortical white matter have been reported in PKU patients [53–55]. In the PKU mouse model, reduced myelin staining in forebrain structures has been reported [38,56,57]. Oligodendroglia, cells that normally synthesize myelin, seem to have adapted to a non-myelinating phenotype in the PKU mouse brain [38]. Berger et al. [50] found myelin proteins to be reduced by 50% compared to controls in a HPA rat model. Dyer et al. [56] reported altered isoform expression of myelin basic protein in PKU mice, and reduced concentrations of myelin basic protein were later reported in untreated PKU mice, which were restored upon dietary Phe-restriction [38].

Alternatively, reduced myelination in PKU may be caused by impaired cholesterol synthesis. Shefer et al. [57] reported reduced activity of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGR), the rate-controlling enzyme of cholesterol synthesis [57]. As cholesterol is one of the primary constituents of myelin lipid, it was hypothesized that decreased HMGR activity may result in reduced myelination in the PKU mouse forebrain and the non-myelinating phenotype of oligodendroglia [57]. However, the reduced HMGR activity reported by Shefer et al. [57] seemed to mainly be caused by reduced HMGR synthesis, suggesting that reduced cerebral protein synthesis may affect enzymes involved in myelin formation.

Regulation of cerebral protein synthesis is essential for brain development and function, as it forms the molecular basis of synaptic plasticity, long-term potentiation, and cognition [58,59]. Deficiencies in the regulation of cerebral protein synthesis may cause mental retardation syndromes in man [58] and therefore could be associated with mental retardation in patients with PKU.

Conclusion

In summary, we hypothesize that the main pathophysiologic mechanisms of cognitive dysfunction in PKU are reduced cerebral neurotransmitter and protein synthesis, caused by impaired brain uptake of non-Phe LNAA in the presence of elevated plasma Phe concentrations. Clearly, more research is needed to investigate these mechanisms in more detail.

Conflict of interest

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