COMMENT

Crosstalk between BH4, pain, and dystonia

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Dystonia is a family of rare disorders, of which several forms are associated with decreased dopamine signaling. Although many genes are recognized as genes linked to dystonia, the major fraction of families suffering from dystonia is without a molecular genetic diagnosis, indicating that additional dystonia-causing genes still needs to be identified. As a result of exome-wide, next-generation sequencing of a large cohort of individuals with dystonia, the gene inosine monophosphate dehydrogenase gene (*IMPDH2*) was in 2020 designated as a new candidate gene, for dominant inherited dystonia. This, despite the fact that the phenotype was primary neurodevelopmental disorder, and dystonia was only expressed in two out of six cases with de novo mutations in the *IMPDH2* gene [1]. By the work from Kuukasjärvi et al. [2] doubts whether *IMPDH2* is associated with dystonia are removed. Kuukasjärvi et al. [2] describe a large family with dominant juvenile-onset dystonia-tremor disorder, in which a truncating variant in *IMPDH2* segregates in the family.

Tetrahydrobiopterin (BH4), is cofactor for tyrosine hydroxylase, the enzyme responsible for synthesis of dopamine, and several genes linked to the synthesis of BH4 has been associated with dystonia (Fig. 1A). BH4 is performed, in three steps using GTP (guanine triphosphate) as precursor. First step; conversion of GTP to 7,8-dihydroneopterin-tripospate is performed by GTP cyclohydrolase 1 (GCH1). The second step is performed by 6-pyruvoyl tetrahydrobiopterin synthase (PTPS) and the third step by sepiapterin reductase (SPR). Disease-causing variants in the genes encoding, GCH1 and SPR have been linked to dopa-responsive dystonia with autosomal dominant and autosomal recessive inherited dopa-responsive dystonia, respectively. IMPDH2 is, as a rate-limiting enzyme for de novo GMP (guanine monophosphate) synthesis; a precursor to GTP, also involved in the biosynthesis of BH4. The enzyme hypoxantine phosphoribosyltransferase (HPRT1) is important for the generation of purine nuclotides (inosine monophosphate (IMP)) and GMP in the salvage pathway, keeping the brain level of GMP. Disease-causing variants in *HRPT1* is associated with Lesh-Nyhan disease, an X-linked severe disorder with neurological dysfunction including dystonia.

About 15 years ago, BH4 was defined, for the first time as a new target for analgesics [3]. It was found that a specific human *GCH1* haplotype, named the pain-protective consisting of 15 single-nucleotide polymorphisms in noncoding regions was associated with reduced pain sensitivity, after pain sensitization performed by for example, capsaicin application. After the first introduction of BH4 as pain-provoking, several reports followed supporting the initial finding, although also papers with conflicting results appeared, indicating that the system might be rather complex. In favor of a possible association with pain, the expression of *GCH1* has been shown to increase during wound healing and increased amount of BH4 has been demonstrated to be produced by neurons and macrophages in damaged nerves and inflamed tissue [3]. Furthermore, chemical or genetically (using antisense mRNA), inhibition of GCH1 or SPR reduce the level of BH4 and alleviates pain behaviors in animal models [4].

Recently, we have investigated the pain sensitivity in individuals with reduced GCH1 activity as a result of disease-causing variants in the *GCH1* gene [4]. The tested individuals were all heterozygous for a loss of function variant in *GCH1* and suffered from dopa-responsive dystonia. Although we could confirm that the BH4 level was reduced in this group of individuals we were to our big surprise not able to see any reduction in experimental pain response after capsaicin-induced pain sensitization. Our hypothesis was that if the pain-protective haplotype, which leads to a modest reduction in BH4 level, was associated with reduced pain sensitivity, then disease-causing variants leading to greatly reduced BH4 concentration must logically lead to a very high pain threshold. But it seems unfortunately not to be the case. The lack of reduced pain sensitivity in patients with pathogenic *GCH1* variants, might indicate that only modest reduction of the BH4 level, might relief the pain sensitivity. In the case of profound reduction of the BH4 level other mechanism might dominate leading to abolition of the pain-relieving effect.

Interesting, self-injurious behavior such as biting of lips, fingers, and cheeks is frequent in individuals with Lesh-Nyhan syndrome, and recent investigations suggest that individuals performing non-suicidal self-injury have an elevated pain tolerance [5].

The observation of hyperalgesia at sensory testing combined with cold hypoesthesia in both legs and cold hyperesthesia on the right shin, in the index patient with a heterozygous truncating variant in *IMPDH2*, described by Kuukasjärvi et al. [2] might indicate that *IMPDH2* also is involved in pain perception. To be able to make any conclusion, several patients and further investigations are needed. Also, the effect on the BH4 concentrations, as a result of loss of function variants in *IMPDH2*, still needs to be investigated. A modest reduction in BH4 might be in favor of pain relief.

Although there is evidence that BH4 is associated with pain perception, the exact mechanism is far from solved. As BH4 is cofactor not only for tyrosine hydroxylase, important for production of dopamine, but also for tryptophan hydroxylase (TPH) and phenylalanine hydroxylase (PAH) important for production of serotonin and tyrosine respectively, and furthermore cofactor for nitric oxide synthase (NOS) important for biosynthesis of nitric oxide (NO) any of the downstream products could be responsible for the pain perception. Thus, whereas reduced dopamine signaling as a result of reduced BH4 concentration seems to responsible for development of dystonia, it might not be responsible for pain perception (Fig. 1B).

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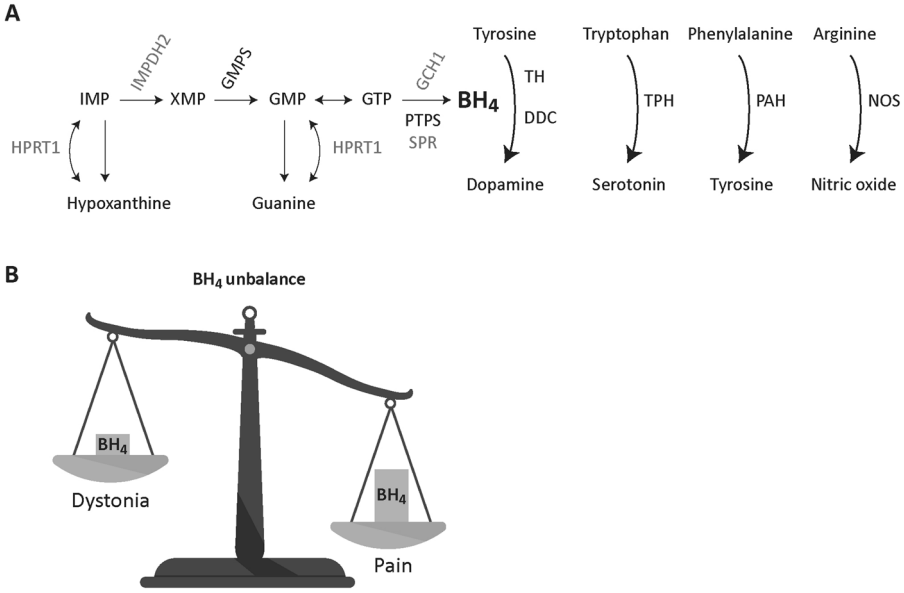

Fig. 1 Biosynthesis and function of BH4. A Several enzymes are involved in the production of dopamine including, IMPDH2, GCH1, SPR, and HRPT1, all associated with dystonia. Inosine monophosphate (IMP), guanine monophosphate/triphosphate (GMP/GTP), guanosine monophosphate synthetase (GMPS), GTP cyclohydrolase 1 (GCH1), 6-pyruvoyl tetrahydrobiopterin synthase (PTPS), sepiapterin reductase (SPR), hypoxantine phosphoribosyltransferase (HPRT1), inosine monophosphate dehydrogenase gene (IMPDH2), tyrosine hydroxylase (TH), aromatic amino acid decarboxylase (DDC), tryptophan hydroxylase (TPH), phenylalanine hydroxylase (PAH), and nitric oxide synthase (NOS). **B** Reduced concentration of BH4 leads to reduced dopamine and dystonia, whereas increased BH4 concentration has been linked to increased pain perception.

Further investigation is needed in order to test if *IMPDH2* could be a potential new target for development of new analgesics.

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COMPETING INTERESTS

The author declares no competing interests.

ADDITIONAL INFORMATION

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