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Minireview

4-Hydroxyphenylpyruvate dioxygenase

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Abstract

4-Hydroxyphenylpyruvate dioxygenase (HPPD) is an Fe(II)-dependent, non-heme oxygenase that catalyzes the conversion of 4-hydroxyphenylpyruvate to homogentisate. This reaction involves decarboxylation, substituent migration and aromatic oxygenation in a single catalytic cycle. HPPD is a member of the α-keto acid dependent oxygenases that typically require an α-keto acid (almost exclusively α-ketoglutarate) and molecular oxygen to either oxygenate or oxidize a third molecule. As an exception in this class of enzymes HPPD has only two substrates, does not use α-ketoglutarate, and incorporates both atoms of dioxygen into the aromatic product, homogentisate. The tertiary structure of the enzyme would suggest that its mechanism converged with that of other α-keto acid enzymes from an extradiol dioxygenase progenitor.

The transformation catalyzed by HPPD has both agricultural and therapeutic significance. HPPD catalyzes the second step in the pathway for the catabolism of tyrosine, that is common to essentially all aerobic forms of life. In plants this pathway has an anabolic branch from homogentisate that forms essential isoprenoid redox cofactors such as plastoquinone and tocopherol. Naturally occurring multi-ketone molecules act as allelopathic agents by inhibiting HPPD and preventing the production of homogentisate and hence required redox cofactors. This has been the basis for the development of a range of very effective herbicides that are currently used commercially. In humans, deficiencies of specific enzymes of the tyrosine catabolism pathway give rise to a number of severe metabolic disorders. Interestingly, HPPD inhibitor/herbicide molecules act also as therapeutic agents for a number of debilitating and lethal inborn defects in tyrosine catabolism by preventing the accumulation of toxic metabolites.

Keywords: Dioxygenase; Oxygenase; Alpha-keto acid; Molecular Oxygen; Inhibitor; 4-Hydroxyphenylpyruvate; Activation; Review; Iron; Ferrous; Non-heme

In aerobic metabolism, the conversion of 4-hydroxyphenylpyruvate (HPP)[1] to 2,5-dihydroxyphenylacetate (homogentisate) is catalyzed by 4-hydroxyphenylpyruvate dioxygenase (HPPD). While this transformation is unique in nature and involves decarboxylation, aromatic hydroxylation, and substituent migration in a single catalytic cycle, the reaction is similar to those catalyzed by the α-keto acid dependent superfamily of oxygenase enzymes [1]. This conversion is the second step of a catabolic pathway that yields acetoacetate and fumarate from L-tyrosine (Scheme 1) [2]. While these ketogenic and glucogenic products have a direct energetic contribution, in higher organisms the pathway serves additional functions. In animals it is required to modulate blood tyrosine levels [3] and in plants the pathway is used for the anabolic production of essential cofactors such as plastoquinone and tocopherol from homogentisate [4]. This latter role for tyrosine catabolism has generated significant research by agrochemical interests who wish to design inhibitors/herbicides that uncouple photosynthesis by suppressing the production of the

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[1] *Abbreviations used:* HPP, 4-hydroxyphenylpyruvate; HPPD, 4-hydroxyphenylpyruvate dioxygenase; PDB, Protien Data Bank; HMS, hydroxy mandelate synthase; NTBC, 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexane dione, MCD, magnetic circular dichroism.

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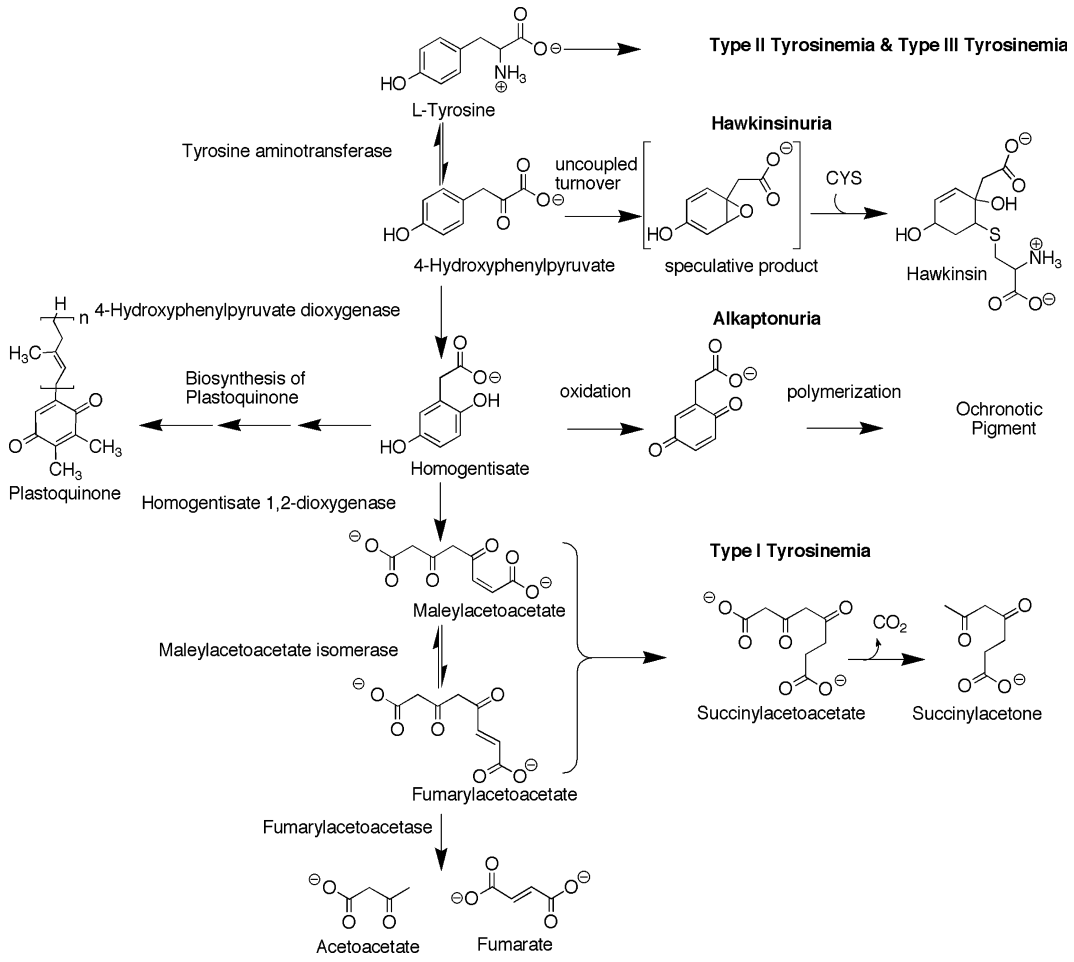

Scheme 1.

redox active lipophilic cofactors that link the two photosystems. Such investigations comprise the majority of the scientific literature for HPPD and have produced a number of commercially available herbicides. Interestingly, one of the early molecules developed as an herbicide is now used therapeutically; the specific inhibition of HPPD is currently used to alleviate the symptoms of two metabolic defects and could conceivably be applied to a third (vide supra). Considerably less research has been undertaken on the chemistry behind the quite extraordinary transformation that yields homogentisate from HPP.

In mammals, inborn defects in tyrosine catabolism give rise to disease states that range in severity from mild to lethal (right side of Scheme 1). A deficiency of the first tyrosine catabolism enzyme, tyrosine aminotransferase, produces type II tyrosinemia, a disease characterized by elevated levels of blood tyrosine that result in mild mental retardation at birth and corneal opacities later in life [5]. Type III tyrosinemia arises from a deficiency of active HPPD [6] and is largely indistinguishable from type II with regard to symptomology due to the reversibility of the preceding tyrosine aminotransferase reaction [7]. Hawkinsinuria is a result of a single mutation in the N-terminal region of the HPPD gene that brings about uncoupled turnover. The mutant enzyme releases an as yet unidentified intermediate/product that becomes covalently linked to thiols such as cysteine and glutathione and is excreted in large quantity in the urine [6]. The primary symptom of this disease is metabolic acidosis, which leads to a host of other deleterious symptoms including severe stunting. The oldest known inherited metabolic disorder is due to deficiency in active homogentisate 1,2-dioxygenase and is known as alkaptonuria [8]. Individuals who suffer from this deficiency accumulate large quantities of the homogentisate hydroquinone which readily oxidizes to the quinone. The reactive quinone can then polymerize to form a structurally uncharacterized caramel colored molecule known as the ochronotic pigment. While excretion of this pigment simply discolors urine without immediate adverse effects, it is the accumulation of it in cartilage and collagenous tissues that gives rise to the chronic debilitating symptoms of arthritic disability [9,10]. Deficiencies of the fourth tyrosine catabolism enzyme, maleylacetoacetate isomerase are not lethal or debilitating due to the propensity of maleylacetoacetate to form both succiny-