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Review

The tryptophan oxidation pathway in mosquitoes with emphasis on xanthurenic acid biosynthesis

Qian Han[a], Brenda T. Beerntsen[b], Jianyong Li[a,*]

[a]Deptment of Biochemistry, Virginia Polytechnic Institute and State University, Blacksburg, VA 24061, USA
[b]Deptment of Veterinary Pathobiology, University of Missouri, 201 Connaway Hall, Columbia, MO 65211, USA

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Abstract

Oxidation of tryptophan to kynurenine and 3-hydroxykynurenine (3-HK) is the major catabolic pathway in mosquitoes. However, 3-HK is oxidized easily under physiological conditions, resulting in the production of reactive radical species. To overcome this problem, mosquitoes have developed an efficient mechanism to prevent 3-HK from accumulating by converting this chemically reactive compound to the chemically stable xanthurenic acid. Interestingly, 3-HK is a precursor for the production of compound eye pigments during the pupal and early adult stages; consequently, mosquitoes need to preserve and transport 3-HK for compound eye pigmentation in pupae and adults. This review summarizes the tryptophan oxidation pathway, compares and contrasts the mosquito tryptophan oxidation pathway with other model species, and discusses possible driving forces leading to the functional adaptation and evolution of enzymes involved in the mosquito tryptophan oxidation pathway.

Keywords: Xanthurenic acid; Mosquito; 3-Hydroxykynurenine; Kynurenine 3-monooxygenase; 3-Hydroxykynurenine transaminase

Contents

*Corresponding author. Tel.: +1 540 231 1182; fax: +1 540 231 9070.
E-mail address: lij@vt.edu (J. Li).

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1. Introduction

Kynurenine and 3-hydroxykynurenine (3-HK) are intermediates in the tryptophan oxidation pathway (Fig. 1). In mammals, kynurenine is the immediate precursor in the pathway leading to the formation of kynurenic acid that serves as a broad-spectrum antagonist at ionotropic excitatory amino acid receptors (NMDA receptors) and protects the central nervous system (CNS) from being overstimulated by excitatory cytotoxins (Stone, 2000). Therefore, there has been extensive research investigating the biochemical pathway leading to the formation of kynurenic acid and the consequences caused by kynurenic acid deficiency (Schwarcz, 1993; Moroni, 1999; Stone, 2001a, c, b). Kynurenine can be oxidized by kynurenine monooxygenase (KMO, EC 1.14.13.9) to form 3-HK. Although 3-HK is a natural metabolite, it is oxidized easily under physiological conditions, stimulating the production of reactive oxygen species (Okuda et al., 1996, 1998; Wei et al., 2000). For example, 3-HK can induce apoptosis of neuron cells at micromolar concentrations (Wei et al., 2000). Injection of tryptophan metabolites into adult flies caused severe motor dysfunction (Cerstiaens et al., 2003). Earlier studies have also shown that 3-HK content was quite different in insects at different developmental stages (Linzen, 1974). To maintain physiological conditions, it is essential to prevent the accumulation of this reactive compound. In mammals, both kynurenine and 3-HK can be hydrolyzed by kynureninase (EC 3.7.1.3) to anthranilic acid and 3-hydroxyanthranilic acid and the latter two compounds can be either completely oxidized to CO_2 and H_2O through a complicated biochemical pathway or used to synthesize $NAD(P)^+$ (Stone, 1993). Although there have been a number of reports discussing the toxicity of 3-HK in mammals (Okuda et al., 1996, 1998; Wei et al., 2000), 3-HK, produced under normal physiological conditions, does not seem to cause any problems in mammals as it can be hydrolyzed and further oxidized via the glutaryl-CoA pathway.

In mosquitoes (likely other insects as well), oxidation of tryptophan to kynurenine and then to 3-HK is a major branch pathway of tryptophan metabolism. However, because mosquitoes do not have kynureninase, the hydrolysis pathway of 3-HK is not available. Consequently, mosquitoes must deal with 3-HK in a different manner. Our study investigating the tryptophan oxidation pathway in *Aedes aegypti* indicated that mosquitoes have developed an efficient strategy to prevent the accumulation of 3-HK by converting the chemically reactive 3-HK to the chemically stable xanthurenic acid (XA) via transaminase-mediated reactions. For example, the concentration of XA is many folds higher than that of 3-HK in the supernatant of mosquito larval homogenate (Li and Li, 1997; Li et al., 1999) (Li, J., unpublished data). As there have been no reports indicating any toxic effect of XA to living organisms, we proposed that the transamination of the chemically reactive 3-HK to the chemically stable XA serves as the mechanism by which mosquitoes detoxify 3-HK (Li and Li, 1997, 1998; Han et al., 2002).

Recently, the 3-HK to XA pathway has attracted increased attention because it has been found that XA induces the exflagellation of *Plasmodium* microgametocytes (Billker et al., 1998; Garcia et al., 1998), an essential step during sexual reproduction of malaria parasites in mosquitoes. Mosquitoes transmit malaria parasites, dengue fever and West Nile virus, which are major threats to human health and well-being throughout the world. Among them, malaria is considered to be the most prevalent life-threatening disease, with estimates of new cases ranging from 300 million to 660 million cases per year (Snow et al.,

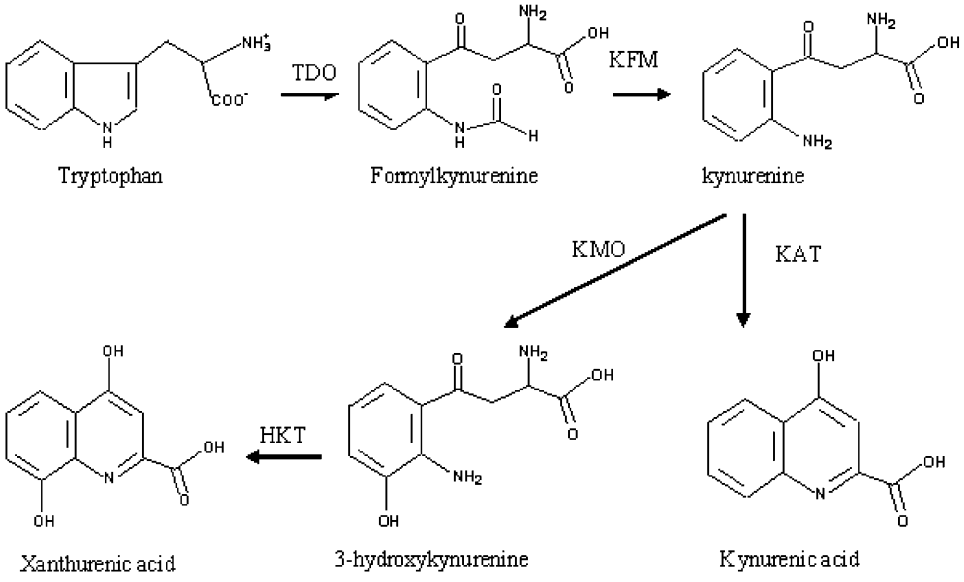

Fig. 1. Biochemical pathway of tryptophan to xanthurenic acid in mosquitoes. TDO, tryptophan dioxygenase; KFM, kynurenine formamidase; KMO, kynurenine monooxygenase; KAT, kynurenine aminotransferase; HKT, 3-hydroxykynurenine transaminase.