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Invited review

Tryptophan availability for kynurenine pathway metabolism across the life span: Control mechanisms and focus on aging, exercise, diet and nutritional supplements

Abdulla A-B. Badawy

School of Health Sciences, Cardiff Metropolitan University, Western Avenue, Llandaff, Cardiff CF5 2YB, Wales, UK

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ABSTRACT

Tryptophan (Trp) availability for the kynurenine pathway (KP) across the life span is discussed. Free (non-albumin-bound) plasma Trp is the major determinant of the flux of Trp down the KP. Flux is the major determinant of kynurenine metabolite formation and is more effective than induction of hepatic Trp 2,3-dioxygenase (TDO) or extrahepatic indoleamine 2,3-dioxygenase (IDO). Flux is better expressed using the sum of plasma kynurenine and its metabolites, rather than kynurenine only. Under normal conditions, TDO controls Trp flux in liver and availability in plasma and can supply kynurenine for the extrahepatic pathway. Under certain pathological conditions associated with immune activation, IDO assumes the major role in control of Trp availability. Plasma Trp availability is increased during pregnancy, at birth, and by exercise, high protein and fat intake. Aging does not seem to exert a major effect on plasma Trp. Assessment of plasma Trp availability in health and disease requires measurement of concentrations of both free and total [Trp] in the first instance, followed, if necessary, by those of albumin and the physiological displacers of albumin-bound Trp, non-esterified fatty acids. Additional measures should include cortisol, cytokines, kynurenine and its metabolites.

This article is part of the Special Issue entitled 'The Kynurenine Pathway in Health and Disease'.

Contents

Abbreviations: 3-HK, 3-Hydroxykynurenine; 3-HAA, 3-hydroxyanthranilic acid; 5-HT, 5-hydroxytryptamine or serotonin; IDO, Indoleamine 2,3-dioxygenase; KA, kynurenic acid; K, kynurenine; NA, nicotinic acid or niacin; PA, picolinic acid; QA, quinolinic acid; Trp, L-tryptophan; TDO, Trp 2,3-dioxygenase; XA, xanthurenic acid.

E-mail address: ABadawy@cardiffmet.ac.uk.

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1. Brief introduction

This article addresses mainly the availability of circulating tryptophan (Trp) for the kynurenine (K) pathway (KP) across the life span. It will cover the stages of life from pregnancy through development to adulthood and old age and discuss issues ranging from control mechanisms to the effects of nutrition, exercise and aging. Each of these issues deserves a full review in its own right. The present article will not therefore be exhaustive, but will hopefully provide sufficient information which can be helpful for future studies of the role of Trp availability in the many clinical and behavioural conditions considered in this special issue of *Neuropharmacology*.

2. Introductory background

2.1. The tryptophan degradative pathways

Less than 1% of dietary Trp is utilised for protein synthesis, because, in a person in nitrogen balance, the amount of Trp degraded is matched by that synthesised (Bender, 1983). The bulk of dietary Trp is therefore metabolised by 4 known pathways, the quantitatively most important of which is the KP. The hepatic KP accounts for ~95% of overall body Trp degradation (Bender, 1983; Badawy, 2002) and contains a complete set of enzymes leading to nicotinamide (vitamin B_3) and NAD^+ synthesis and complete oxidation of Trp to CO_2 and water. Extrahepatically, the KP is widely distributed and, although its contribution to Trp degradation under normal conditions is small, it can assume major significance under conditions of immune activation. Of the 3 other degradative pathways, the hydroxylation or serotonin pathway is the smallest. Urinary excretion studies of the major serotonin metabolite 5-hydroxyindol-3-ylacetic acid (5-HIAA), as a measure of overall body serotonin synthesis and turnover, suggest that only 1% of dietary Trp is metabolised via this pathway (Michael et al., 1964), with the cerebral pathway being a small part thereof. The decarboxylation (to tryptamine) and transamination (to indol-3-ylpyruvic acid) pathways are relatively more active (Green et al., 1980; Huether et al., 1992).

2.2. The kynurenine pathway

Although enzymes of the KP will be discussed elsewhere in this issue, a brief description of the pathway will be made here in relation to Trp availability. Also, as the initial enzymes in the hepatic and extrahepatic pathways are the first to come into contact with Trp and control its availability under physiological and certain pathological conditions, their regulatory mechanisms and catalytic properties will be discussed and, where appropriate, changes in their activities in the conditions listed below across the life span will be briefly described.

In the KP (Fig. 1), the pyrrole moiety of *L*-Trp is opened by Trp 2,3-dioxygenase (TDO, formerly Trp pyrrolase: EC.1.13.11.11) in liver and indol-3-ylamine 2,3-dioxygenase (IDO: EC.1.13.11.17) elsewhere, and the product is hydrolyzed to kynurenine (K) by *N*-formylkynurenine formamidase. K is mainly hydroxylated 3-hydroxykynurenine (3-HK), which is further hydrolyzed by kynureninase to 3-hydroxyanthranilic acid (3-HAA). K can also be converted to anthranilic acid by kynureninase. Transamination of K and 3-HK to kynurenic acid (KA) and xanthurenic acid (XA)