Neuropharmacology 112 (2017) 373–388

Contents lists available at ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

Invited review

Recent evidence for an expanded role of the kynurenine pathway of tryptophan metabolism in neurological diseases

Michael D. Lovelace [a, b], Bianca Varney [a], Gayathri Sundaram [a], Matthew J. Lennon [a], Chai K. Lim [d], Kelly Jacobs [d], Gilles J. Guillemin [d], Bruce J. Brew [a, b, c, *]

[a] Peter Duncan Neurosciences Research Unit, St Vincent's Centre for Applied Medical Research, 405 Liverpool Street, Darlinghurst, Sydney, NSW, 2010, Australia
[b] St Vincent's Clinical School, Faculty of Medicine, University of NSW, Sydney, Australia
[c] Department of Neurology, St Vincent's Hospital, Level 4 Xavier Building, Victoria Street, Darlinghurst, Sydney, NSW, 2010, Australia
[d] Neuroinflammation Group, Faculty of Medicine and Health Sciences, Macquarie University, Sydney, Australia

ARTICLE INFO

Article history:
Received 20 November 2015
Received in revised form
10 March 2016
Accepted 12 March 2016
Available online 16 March 2016

Keywords:
Kynurenine pathway
Neuroinflammation
Neurodegenerative disease
HIV-acquired neurodeficit disorder

ABSTRACT

The kynurenine pathway (KP) of tryptophan metabolism has emerged in recent years as a key regulator of the production of both neuroprotective (e.g. kynurenic and picolinic acid, and the essential cofactor NAD+) and neurotoxic metabolites (e.g. quinolinic acid, 3-hydroxykynurenine). The balance between the production of the two types of metabolites is controlled by key rate-limiting enzymes such as indoleamine-2,3-dioxygenase (IDO-1), and in turn, molecular signals such as interferon-γ (IFN-γ), which activate the KP metabolism of tryptophan by this enzyme, as opposed to alternative pathways for serotonin and melatonin production. Dysregulated KP metabolism has been strongly associated with neurological diseases in recent years, and is the subject of increasing efforts to understand how the metabolites are causative of disease pathology. Concurrent with these endeavours are drug development initiatives to use inhibitors to block certain enzymes in the pathway, resulting in reduced levels of neurotoxic metabolites (e.g. quinolinic acid, an excitotoxin and *N*-Methyl-D-Aspartate (NMDA) receptor agonist), while in turn enhancing the bioavailability of the neuroprotective metabolites such as kynurenic acid. Neurodegenerative diseases often have a substantial autoimmune or inflammatory component; hence a greater understanding of how KP metabolites influence the inflammatory cascade is required. Additionally, challenges exist in diseases like multiple sclerosis (MS) and motor neurone disease (MND), which do not have reliable biomarkers. Clinical diagnosis can often be prolonged in order to exclude other diseases, and often diagnosis occurs at an advanced state of disease pathology, which does not allow a lengthy time for patient assessment and intervention therapies. This review considers the current evidence for involvement of the KP in several neurological diseases, in biomarkers of disease and also the parallels that exist in KP metabolism with what is known in other diseases such as HIV, Alzheimer's disease/dementia, infection, immune privilege and cardiovascular disease.

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

Contents

* Corresponding author. Peter Duncan Neurosciences Research Unit, St Vincent's Centre for Applied Medical Research, Department of Neurology, Level 4 Xavier Building, St Vincent's Hospital, Victoria Street, Darlinghurst, Sydney, 2010, Australia.
E-mail address: b.brew@unsw.edu.au (B.J. Brew).

http://dx.doi.org/10.1016/j.neuropharm.2016.03.024
0028-3908/

1. Introduction

Tryptophan (TRP) is an essential amino acid and precursor for the synthesis of proteins, nicotinamide adenine dinucleotide (NAD), nicotinic acid and the neurotransmitter serotonin (Oxenkrug, 2007). TRP is metabolized through two major pathways, the kynurenine pathway (KP) and the methoxyindole pathway. The methoxyindole pathway generates serotonin (5-hydroxytryptamine), which is a further substrate for melatonin biosynthesis (Oxenkrug, 2011). This pathway accounts for approximately 5% of TRP metabolism. The other 95% of TRP is catabolized through the KP, which is the focus of this review. Historically the importance of the KP was attributed to the production of the cofactor NAD, which has essential roles in several biological processes such as redox reactions essential for mitochondrial function (Jones et al., 2013). However, following the finding that alterations of TRP metabolism are found in a plethora of central nervous system (CNS) diseases, there has been a shift in focus to the enzymes and the metabolites they produce, collectively called the kynurenines. Since then, the KP has been implicated in a wide range of pathophysiologies that encompass neurodegenerative, neurological, neurogenesis and even psychiatric disorders such as schizophrenia and depression.

Furthermore, the effects of the KP are not just limited to the CNS, and have been investigated in the vasculature, infections, transplant rejection, allergies, cancer immunity, autoimmunity and immunological tolerance of the fetus (Moroni, 1999; Guillemin et al., 2007; Guillemin, 2012; Vecsei et al., 2013). In this review, following a brief introduction of the neuroactive metabolites of the KP, we describe peripheral and brain sources of kynurenines. We then focus on their role in the pathophysiology of neurodegeneration, inflammation and the immune response in disease states, using specific examples from the CNS and peripheral organs. This review importantly aims to bring together recent evidence of KP involvement in disorders affecting multiple tissues and organs, and as such, a number of important disorders such as psychiatric diseases are not discussed in detail. Finally, we finish with a summary of recent and exciting new updates in emerging therapeutic and clinical applications that target the KP.

2. The kynurenine pathway

In blood, up to 90% of TRP circulates in an unbound form while the other 10% is bound to albumin, with these two states existing in equilibrium. However, only TRP in its free form can be transported across the blood-brain barrier (BBB) with the aid of the non-specific and competitive L-type amino acid transporter (Jones et al., 2013). The KP represents the primary route of TRP catabolism for both the CNS and the periphery. Following the KP, TRP is converted to *N*-formyl-L-kynurenine by indoleamine-2,3-dioxygenase (IDO-1 and 2), and tryptophan 2,3-dioxygenase 2 (TDO); the rate-limiting enzyme in TRP degradation. TDO is strongly and constitutively expressed in the liver, and is thought to be contribute to systemic levels of TRP (Miller et al., 2004). However it is also expressed at lower levels in neurons, astrocytes and endothelial cells, and more recently found in tumours instead of, or addition to IDO-1 (Guillemin et al., 2007; Platten et al., 2014). Extra-hepatically, IDO-1 is the predominant enzyme in several different cell types including monocytes, macrophages, microglia, astrocytes, neurons and in some stem cells (Guillemin et al., 2007; Jones et al., 2013; Ling et al., 2014). IDO-1 is up regulated by inflammatory molecules and cytokines, such as amyloid peptides, lipopolysaccharides (LPS) and most potently by interferon-γ (IFN-γ), which induces both the enzymatic activity and gene expression of IDO-1 (Shimizu et al., 1978; Yasui et al., 1986; Werner-Felmayer et al., 1989). IDO-2 possesses similar enzymatic and structural characteristics to IDO-1, however is basally expressed in a narrow range of cell types, which suggests its functional role is inferior to that of IDO-1 (Ball et al., 2007). Increasing evidence supports additional roles of IDO-2 in humans in shaping immune tolerance and in tolerance for "altered-self" antigens in autoimmunity (reviewed in ((Prendergast et al., 2014). Proceeding along the KP, *N*-formyl-L-kynurenine is metabolised to L-kynurenine (KYN), the first stable intermediate metabolite, by formamidase (Fig. 1). In the CNS, approximately 60% of KYN present crosses the BBB, and 40% is locally produced (Vecsei et al., 2013). KYN is central metabolite of the KP, and can be catabolised through three specific pathways (Fig. 1) to generate anthranilic acid (AA), 3-hydroxy-L-kynurenine and kynurenic acid (KYNA) by the enzymes kynureninase (KYNU), kynurenine 3-monooxygenase (KMO) and kynurenine aminotransferase (KAT), respectively (Schwarcz, 2004). Further catabolism of 3-hydroxy-L-kynurenine can lead to the formation of the neurotoxic metabolites quinolinic