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Invited review

# Stress-related regulation of the kynurenine pathway: Relevance to neuropsychiatric and degenerative disorders

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ABSTRACT

The kynurenine pathway (KP), which is activated in times of stress and infection has been implicated in the pathophysiology of neurodegenerative and psychiatric disorders. Activation of this tryptophan metabolising pathway results in the production of neuroactive metabolites which have the potential to interfere with normal neuronal functioning which may contribute to altered neuronal transmission and the emergence of symptoms of these brain disorders. This review investigates the involvement of the KP in a range of neurological disorders, examining recent *in vitro*, *in vivo* and clinical discoveries highlights evidence to indicate that the KP is a potential therapeutic target in both neurodegenerative and stress-related neuropsychiatric disorders. Furthermore, this review identifies gaps in our knowledge with regard to this field which are yet to be examined to lead to a more comprehensive understanding of the role of KP activation in brain health and disease.

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



**Contents**



*Abbreviations:* 3-HAO, 3-hydroxyanthranilic acid 3, 4-dioxygenase; ACMSD, aminocarboxymuconate semialdehyde decarboxylase; AhR, aryl hydrocarbon receptor; AMPA, α-amino-3-hydroxyl-5-methyl-4-isoxazolepropionic acid; BBB, blood brain barrier; BDNF, brain derived neurotrophic factor; cAMP, cyclic adenosine monophosphate; CNS, central nervous system; COX, cyclooxygenase; CREB, cAMP response element binding; FST, forced swimming test; GPR35, g-protein coupled receptor 35; GR, glucocorticoid receptor; HPA, hypothalamic adrenal; IDO, indoleamine 2, 3-dioxygenase; IFN, interferon; KAT, kynurenine aminotransferase; KMO, kynurenine monooxygenase; KP, kynurenine pathway; KYNA, kynurenic acid; KYNU, kynureninase; LPS, lipopolysaccharide; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; $NAD^+$, nicotinamide adenine dinucleotide; NMDA, N-methyl-D-aspartate; OCD, obsessive compulsive disorder; PKA, protein kinase A; POLY I:C, polyinositolphosphatidic acid; QPRT, quinolinate phosphoribosyl transferase; PTSD, post-traumatic stress disorder; ROS, reactive oxygen species; SAM, sympathoadrenal medullary; TDO, tryptophan 2, 3-dioxygenase; TGF, transforming growth factor; TMF, 6,2′,4′-trimethoxyflavone.

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## 1. Introduction

The kynurenine pathway (KP) is a tryptophan metabolism pathway that is induced in times of stress and or immune activation. Initially tryptophan is converted to kynurenine which is subsequently converted into a range of metabolites which have neuromodulatory properties (Fig. 1). The pathway has been implicated in the pathophysiology of multiple central nervous system (CNS) disorders ranging from psychiatric disorders to neurodegenerative diseases (Reus et al., 2015; Bohar et al., 2015; Karakuła-Juchnowicz et al., 2015). Its likely contribution to underlying mechanisms associated with CNS disorders indicates that regulation of the KP is of critical importance and may serve as an important target for the future development of treatments for a range of CNS-related illnesses.

## 2. The differential activation and roles of IDO and TDO

Both TDO and IDO have evolved to have similar functions, differing primarily in substrate specificity and tissue and cellular localisation. Most species contain both tryptophan-metabolising enzymes, with gene duplications resulting in certain species having several homologs of these enzymes (Ball et al., 2014). IDO is a monomeric enzyme with a broader substrate specificity than TDO. IDO and TDO have a sequence identity of only 10%, while the recently discovered tryptophan-catabolising enzyme IDO-2 which is encoded by a gene adjacent to that of IDO, shares 43% sequence identity and structural similarities with IDO (Forouhar et al., 2007). IDO is expressed extra-hepatically in intestinal, lung, placenta and brain tissue (Stone, 1993) with high expression of IDO found in the spleen as a consequence of the accumulation of IDO-expressing immune cells, including dendritic cells and peripheral blood mononuclear cells (Jones et al., 2015; Bronte and Pittet, 2013; Hwu et al., 2000).

### 2.1. The role of IDO in KP activation

Induction of IDO is pivotal in the immune response. IDO activation is associated with the anti-parasitic, anti-fungal, anti-viral and anti-bacterial activities of polymorphonuclear immune cells (Bozza et al., 2005; Kwidzinski and Bechmann, 2007). These effects are achieved through tryptophan depletion and the production of kynurenine, 3-hydroxykynurenine, and 3-hydroxyanthranilic acid in pathogens which are anti-proliferative and increase the apoptotic susceptibility of the cells in which they are produced. Moreover, activation of IDO results in immunosuppression and can lead to immune tolerance (Kwidzinski and Bechmann, 2007) if the aforementioned mechanisms occur in T lymphocytes (Fallarino et al., 2002). The KP metabolites also shift the T cell response towards the development of regulatory T cells. This occurs as a consequence of a positive feedback cycle which exists between dendritic cells and regulatory T cells, in so much as IDO induction in dendritic cells drives the development of $CD4^+$ T cells towards the regulatory T cell phenotype, which further induces IDO in dendritic cells (Hill et al., 2007). In addition, 3-hydroxyanthranilic acid triggers the production of transforming growth factor β (TGFβ) which further promotes the development of regulatory T cells, alongside suppressing the development of $Th_1$ cells (Munn, 2011).

In the CNS, IDO is expressed in neurons, macrophages, microglia and astrocytes, but not oligodendrocytes (Lim et al., 2010). Neurons express both IDO and IDO-2 which exhibit a reciprocal relationship with TDO expression, in that induction of IDO results in decreased expression of TDO (Guillemin et al., 2007). IDO-2 is present in different tissues to that of IDO, such as the epididymis, liver and kidneys (Fukunaga et al., 2012; Ball et al., 2007) indicating that it is not functionally redundant. However, the neurological and immune effects of IDO-2 are not fully elucidated and its function in human cells is unknown (Vecsei et al., 2013; Fatokun et al., 2013). Moreover, IDO-2 appears to be much less enzymatically active than IDO as indicated by its lower substrate binding affinity and lower turnover rates (Pantouris et al., 2014).

Activation of the sympathoadrenal medullary (SAM) axis following exposure to stress leads to the release of noradrenaline from sympathetic nerve endings and adrenaline from the adrenal medulla. Catecholamines activate β-adrenergic receptors expressed on natural killer cells, T cells, B cells and monocytes (Maisel et al., 1989) which results in the expression and release of pro-inflammatory cytokines, specifically interferon-γ (IFNγ), IL-1β and IL-6 which are capable of inducing IDO (Elenkov et al., 2000; see, Kohm and Sanders (2001) for review). Inflammation is also capable of activating the downstream KP enzyme KMO (Connor et al., 2008), which is a flavin adenine dinucleotide dependent monooxygenase enzyme (Alberati-Giani et al., 1997), located in the outer mitochondrial membrane (Erickson et al., 1992). KMO is expressed peripherally in the kidney and liver as well as in the brain where it is primarily found in microglia (Guillemin et al., 2005b), with low expression of it in neurons (Guillemin et al., 2007).

### 2.2. The role of TDO in KP activation

TDO is a homotetrameric enzyme with its expression primarily restricted to the liver in the periphery (Stone, 1993) while it is