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Review

Genetic alterations affecting the genes encoding the enzymes of the kynurenine pathway and their association with human diseases

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ABSTRACT

Tryptophan is metabolized primarily *via* the kynurenine pathway (KP), which involves several enzymes, including indoleamine 2,3-dioxygenase, tryptophan 2,3 dioxygenase (TDO), kynurenine aminotransferases (KATs), kynurenine monooxygenase (KMO) etc. The majority of metabolites are neuroactive: some of them, such as kynurenic acid, show neuroprotective effects, while others contribute to free radical production, leading to neurodegeneration. Imbalance of the pathway is assumed to contribute to the development of several neurodegenerative diseases, psychiatric disorders, migraine and multiple sclerosis.

Our aim was to summarize published data on genetic alterations of enzymes involved in the KP leading to disturbances of the pathway that can be related to different diseases.

To achieve this, a PubMed literature search was performed for publications on genetic alterations of the KP enzymes upto April 2017.

Several genetic alterations of the KP have been identified and have been proposed to be associated with diseases. Here we must emphasize that despite the large number of recognized genetic alterations, the number of firmly established causal relations with specific diseases is still small. The realization of this by those interested in the field is very important and finding such connections should be a major focus of related research.

Polymorphisms of the genes encoding the enzymes of the KP have been associated with autism, multiple sclerosis and schizophrenia, and were shown to affect the immune response of patients with bacterial meningitis, just to mention a few.

To our knowledge, this is the first comprehensive review of the genetic alterations of the KP enzymes. We believe that the identification of genetic alterations underlying diseases has great value regarding both treatment and diagnostics in precision medicine, as this work can promote the understanding of pathological mechanisms, and might facilitate medicinal chemistry approaches to substitute missing components or correct the disturbed metabolite balance of KP.

1. Introduction

1.1. A general overview of the kynurenine pathway

Most of the dietary tryptophan (Trp) not used for protein synthesis is metabolized *via* the kynurenine pathway (KP) [1]. The metabolites have a broad spectrum of biological actions, and have been connected to several diseases [2–5]. The KP is one branch of Trp metabolism; the other branch provides serotonin and melatonin (Fig. 1). The first step in the KP is the conversion of Trp to N-formyl-L-kynurenine, by tryptophan

Abbreviations: KP, kynurenine pathway; IDO, indoleamine 2,3-dioxygenase; TDO2, tryptophan 2,3 dioxygenase (gene); TDO, tryptophan 2,3 dioxygenase (enzyme); KAT, kynurenine aminotransferase; KMO, kynurenine monooxigenase; Trp, tryptophan; KYN, L-kynurenine; KYNA, kynurenic acid; 3-HK, 3-hydroxykynurenine; KYNU, kynureninase; AA, anthranilic acid; XA, xanthurenic acid; 3-HAA, 3-hydroxyanthranilate; ACMSD, aminocarboxymuconate-semialdehyde decarboxylase; QUIN, quinolinic acid; NAD+, nicotinamide-adenine-dinucleotide; GWAS, genome wide association studies; SNP, single nucleotide polymorphisms; LPS, lipopolysaccharides; TNF, tumor necrosis factor; IFN, interferon; MDD, major depressive disorder; CD, Crohn's disease; PDA, pancreatic ductal adenocarcinoma; TS, Tourette syndrome; ADHD, attention deficit hyperactivity disorder; GC, glucocorticoid; GRE, glucocorticoid responsive element; GR, glucocorticoid receptor; AADAT, aminoadipate aminotransferase; HD, Huntington's disease; AD, Alzheimer's disease; PD, Parkinson's disease; MS, multiple sclerosis; NMDS, N-methyl-D-aspartate; BM, bacterial meningitis; MIP-1αCCL3, macrophage inflammatory protein 1-alpha; MIP-1βCCL4, macrophage inflammatory protein-1-beta; CSF, cerebrospinal fluid; HO-1, hemeoxygenase-1; NO-cGMP, nitric oxide – cyclic guanosine monophosphate; PFC, prefrontal cortex; PDS, postpartum depressive symptoms; 3-OHKYN, 3-hydroxykynurenine; SHR, spontaneously hypertensive rat; 3-HAO, 3-hydroxyanthranilate 3,4-dioxygenase; COGA, Collaborative Study on the Genetics of Alcoholism; FCMTE, familial cortical myoclonic tremor and epilepsy; WGS, whole genome sequencing

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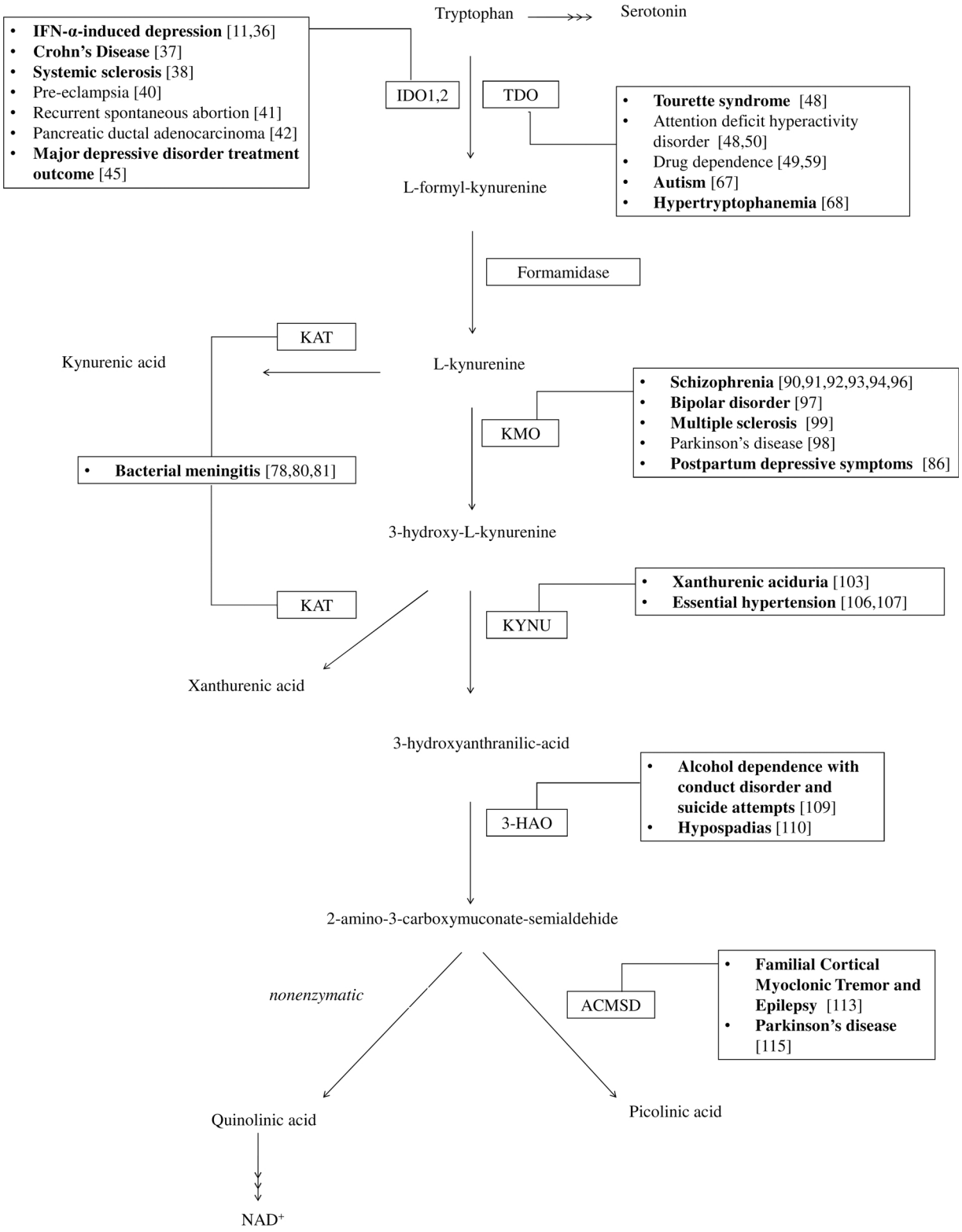

Fig. 1. An overview of the KP. The metabolites are indicated with full name. The names of the enzymes are given in abbreviated forms. Diseases for which association of genetic alteration(s) resulting in malfunction of a particular enzyme has been investigated are listed with references. (Bold: association have been found). Abbreviations: IDO1,2: Indoleamine-2,3-dioxygenase 1,2; TDO: Tryptophan 2,3-dioxygenase; KAT: Kynurenine aminotransferase; KMO: Kynurenine 3-monooxygenase/Kynurenine 3-Hydroxylase; KYNU: Kynureninase/L-Kynurenine Hydrolase; 3-HAO: 3-hydroxyanthranilate 3,4-dioxygenase; ACMSD: Aminocarboxymuconate semialdehyde decarboxylase/Picolinate carboxylase; NAD+: Nicotinamide adenine dinucleotide.

2,3-dioxygenase (TDO) or indoleamine 2,3-dioxygenase (IDO). Formamidase converts N-formyl-L-kynurenine to L-kynurenine (KYN), which can be further metabolized by three distinct pathways. Kynurenine aminotransferases (KATs) can convert KYN to kynurenic acid (KYNA), kynurenine 3-monooxygenase (KMO) can convert it to 3-hydroxykynurenine (3-HK), while kynureninase (KYNU) converts it to