Neuropharmacology 112 (2017) 331–345

Contents lists available at ScienceDirect

Neuropharmacology

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

Invited review

Kynurenine pathway metabolites and enzymes involved in redox reactions

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ARTICLE INFO

Article history:
Received 16 October 2015
Received in revised form
28 February 2016
Accepted 6 March 2016
Available online 10 March 2016

Keywords:
Kynurenines
Oxidative damage
Mitochondria dysfunction
Redox homeostasis

ABSTRACT

Oxido-reduction reactions are a fundamental part of the life due to support many vital biological processes as cellular respiration and glucose oxidation. In the redox reactions, one substance transfers one or more electrons to another substance. An important electron carrier is the coenzyme NAD^+, which is involved in many metabolic pathways. De novo biosynthesis of NAD^+ is through the kynurenine pathway, the major route of tryptophan catabolism, which is sensitive to redox environment and produces metabolites with redox capacity, able to alter biological functions that are controlled by redox-responsive signaling pathways. Kynurenine pathway metabolites have been implicated in the physiology process and in the physiopathology of many diseases; processes that also share others factors as dysregulation of calcium homeostasis, mitochondrial dysfunction, oxidative stress, inflammation and cell death, which impact the redox environment. This review examines in detail the available evidence in which kynurenine pathway metabolites participate in redox reactions and their effect on cellular redox homeostasis, since the knowledge of the main factors and mechanisms that lead to cell death in many neurodegenerative disorders and other pathologies, such as mitochondrial dysfunction, oxidative stress and kynurenines imbalance, will allow to develop therapies using them as targets.

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

Contents

Abbreviations: ACMSD, 2-amino-3-carboxymuconate-6-semialdehyde decarboxylase; ATP, adenosine triphosphate; ANA, anthranilic Acid; DHQCA, 4,6-dihydroxyquinoline quinone carboxylic acid; H_2O_2, hydrogen peroxide; IDO, indoleamine 2,3-dioxygenase; KATs, kynurenine aminotransferases; KMO, kynurenine 3-monooxygenase; KP, kynurenine pathway; KYNA, kynurenic acid; L-KYN, L-kynurenine; NAD^+, nicotinamide adenine dinucleotide; NADPH, nicotinamide adenine dinucleotide phosphate; NFK, N-formylkynurenine; NOS, nitric oxide synthase; O_2, oxygen; $O_2^{\bullet-}$, superoxide anion; PIC, picolinic acid; P5P, pyridoxal-5'-phosphate; QPRTase, quinolinate phosphoribosyltransferase; QUIN, quinolinic acid; RNS, Reactive nitrogen species; ROS, Reactive oxygen species; SOD, superoxide dismutase; TDO, tryptophan 2,3-dioxygenase; TRP, tryptophan; XA, xanthurenic acid.

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http://dx.doi.org/10.1016/j.neuropharm.2016.03.013
0028-3908/

1. Cellular redox homeostasis

Oxidation-reduction reactions are intimately connected with the functioning of the natural environment; however, imbalance of these reactions can influence this cellular environment and provoke loss of cellular redox homeostasis, leading to major consequences on cell functions, considering that various cellular signaling pathways and stress reaction systems are sensitive to redox situation (Chiu and Dawes, 2012).

A free radical is a very reactive atom with an unpaired electron in its outer orbits, property that makes it highly reactive. There are other molecules without free electrons in their outer orbits but are highly reactive, named non-free radicals. Both, free radicals and non-free radicals are collectively called as reactive species. During the cellular processes, reactive oxygen species (ROS) and reactive nitrogen species (RNS) are produced (Dawane and Pandit, 2012). When the production of ROS and RNS overwhelm the scavenging capacity of cellular antioxidant systems, cells enter in oxidative stress causing cell damage to macromolecules. Oxidative stress is involved in many neurodegenerative diseases due to propagation of cell damage in the brain, which is especially sensitive to it and it is also the main energy consumer tissue.

Redox state is one of the main factors able to regulate many metabolic reactions (Atkinson, 1969), considering that, the majority of metabolites in biochemical pathways act as donors and acceptors of electrons. The most common free radicals that produce damage to biological organisms are derived from oxygen, due to the important oxygen role in the respiratory chain for ATP production, taking place in the mitochondria. The impairment of any of the complexes involved in the oxidative phosphorylation chain increases production of free radicals enhancing the damage to macromolecules (Emerit et al., 2004), producing misfolded proteins, lipid peroxidation, nucleic acid damage and also changes in the cellular signaling pathways sensitive to redox environment (Emerit et al., 2004; Szalardy et al., 2015). ROS are also derived from P450 enzymes, due to during biochemical transformations is used O_2 that later generates ROS (metabolism and catabolism), and from inflammatory cell activation. Cerebral inflammatory reactions are present in neurodegenerative diseases, as protective mechanism, releasing several cell factors such as proinflammatory cytokines, prostaglandins and neurotrophic factors, ROS and NOS, micro ambient that if is maintained for a long time, contributes to cell damage and death. But ROS also have a physiological role at low concentrations levels (Russell and Cotter, 2015). They participate in many enzyme process and are produced by several enzymes as xanthine oxidase, NADPH oxidase and nitric oxide synthase, performing important signaling functions in mammalian cells, such as redox-sensitive intracellular signaling pathways generated from NADPH oxidase, gene expression, induction of transcription factors, defense, biosynthesis of molecules that participate in developmental process, cellular growth and aging among others (Dan Dunn et al., 2015; Mariani et al., 2005).

As previously was mentioned, mitochondria are the major source of ROS and the maintenance of redox homeostasis in this organelle is important for the protection of essential redox-sensitive cellular process (Lill and Muhlenhoff, 2008). One important cofactor for redox environment is NAD^+ and its reduced form NADH (Ussher et al., 2012). NAD^+ and NADH are used during cellular respiration, oxidative phosphorylation and ATP production. In fact, ATP synthesis and redox potential are directly proportional to intracellular NAD^+ concentrations (Ussher et al., 2012). In mammals, de novo biosynthesis of NAD^+ is through tryptophan catabolism by the kynurenine pathway. Many enzymes of this pathway are modulated by the redox environment, but also the metabolites produced during the tryptophan (TRP) degradation possess redox properties, which can modify redox homeostasis. Recently, alterations in KP have been involved in many diseases that also present changes on cellular homeostasis since exhibits mitochondrial dysfunction and oxidative stress.

2. Kynurenine pathway (KP)

Tryptophan is an essential amino acid, required for protein synthesis but is also the precursor of several important substances such as serotonin, melatonin and niacin. TRP is metabolized following different routes which produce important biologically compounds. The main metabolism routes are the kynurenine pathway (KP) and the serotonin pathway which is more known, producing 5-hydroxytryptophan and then serotonin, and is present in platelets and neurons (Sas et al., 2007). TRP also produce melatonin, a pineal hormone.

The KP is the most important route considering that 95% of TRP is metabolized in the liver leading to the biosynthesis of NAD^+, a coenzyme that participate in many cellular processes (Fig. 1). The KP have several enzymes that degrades TRP and the most important have been widely studied in rodents and mammals (Wolf, 1974). NAD^+ is reversibly converted to NADH by the addition of two electrons and one proton to the nicotinamide ring.