Ageing Research Reviews 27 (2016) 93–107

Contents lists available at ScienceDirect

Ageing Research Reviews

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

Review

Roles of the tyrosine isomers *meta*-tyrosine and *ortho*-tyrosine in oxidative stress

Brett R. Ipson[a,b,c], Alfred L. Fisher[c,d,e,*]

[a] MD/PhD Program, University of Texas Health Science Center at San Antonio, San Antonio, TX, United States
[b] Department of Cell and Structural Biology, Graduate School of Biomedical Sciences, University of Texas Health Science Center at San Antonio, San Antonio, TX, United States
[c] Center for Healthy Aging, University of Texas Health Science Center at San Antonio, San Antonio, TX, United States
[d] Department of Medicine, Division of Geriatrics, Gerontology, and Palliative Medicine, University of Texas Health Science Center at San Antonio, San Antonio, TX, United States
[e] GRECC, South Texas VA Health Care System, San Antonio, TX, United States

ARTICLE INFO

Article history:
Received 5 January 2016
Received in revised form 20 March 2016
Accepted 30 March 2016
Available online 31 March 2016

Keywords:
meta-Tyrosine
ortho-Tyrosine
Tyrosine isomers
Oxidative stress
Hydroxyl radical
Aging

ABSTRACT

The damage to cellular components by reactive oxygen species, termed oxidative stress, both increases with age and likely contributes to age-related diseases including Alzheimer's disease, atherosclerosis, diabetes, and cataract formation. In the setting of oxidative stress, hydroxyl radicals can oxidize the benzyl ring of the amino acid phenylalanine, which then produces the abnormal tyrosine isomers *meta*-tyrosine or *ortho*-tyrosine. While elevations in *m*-tyrosine and *o*-tyrosine concentrations have been used as a biological marker of oxidative stress, there is emerging evidence from bacterial, plant, and mammalian studies demonstrating that these isomers, particularly *m*-tyrosine, directly produce adverse effects to cells and tissues. These new findings suggest that the abnormal tyrosine isomers could in fact represent mediators of the effects of oxidative stress. Consequently the accumulation of *m*- and *o*-tyrosine may disrupt cellular homeostasis and contribute to disease pathogenesis, and as result, effective defenses against oxidative stress can encompass not only the elimination of reactive oxygen species but also the metabolism and ultimately the removal of the abnormal tyrosine isomers from the cellular amino acid pool. Future research in this area is needed to clarify the biologic mechanisms by which the tyrosine isomers damage cells and disrupt the function of tissues and organs and to identify the metabolic pathways involved in removing the accumulated isomers after exposure to oxidative stress.

Published by Elsevier B.V.

Contents

* Corresponding author at: Department of Medicine, Division of Geriatrics, Gerontology, and Palliative Medicine, 8403 Floyd Curl Drive, room 292.3, San Antonio, TX, United States.
E-mail address: Fishera2@uthscsa.edu (A.L. Fisher).

http://dx.doi.org/10.1016/j.arr.2016.03.005
1568-1637/Published by Elsevier B.V.

1. Introduction

Since 1956 when Denham Harman first postulated that aging and its associated diseases could be attributed to cellular damage caused by free radicals (Harman, 1956), the Free Radical Theory of Aging has been a central hypothesis in aging research. Extensive research has been conducted to determine the role of reactive oxygen species in the aging process, and arguments both for and against this hypothesis have been put forth (Buffenstein et al., 2008; Hekimi et al., 2011; Perez et al., 2009; Schaar et al., 2015; Vina et al., 2013). In seemingly direct conflict to this theory, multiple reports have shown the knockdown of key anti-oxidative genes and/or the increase of reactive oxygen species within an organism not only fail to shorten lifespan, but in some cases increase it altogether (Doonan et al., 2008; Schulz et al., 2007; Van Raamsdonk and Hekimi, 2012). Yet the damage to cellular components by reactive oxygen and nitrogen species, termed oxidative stress, has also been reported to increase with age (Stadtman, 1992) and is likely to contribute to age-related diseases including Alzheimer's disease (Shen et al., 2008; Tamagno et al., 2002, 2008; Wang et al., 2014), atherosclerosis (Li et al., 2014; Pennathur et al., 2001), diabetes (Brownlee, 2001; Giacco and Brownlee, 2010), and cataract formation (Fu et al., 1998b; Kruk et al., 2015). These discrepancies highlight the limited understanding we currently have regarding oxidative stress and the processes by which it mediates cell damage and contributes to aging and disease. With abnormal tyrosine isomers as an example, it is likely that many of the pathological mechanisms of oxidative stress occur insidiously and extend far beyond our current knowledge.

Under conditions of oxidative stress, the production of the abnormal tyrosine isomers *meta*- and *ortho*-tyrosine primarily occurs when hydroxyl radicals oxidize the benzyl ring of phenylalanine (Mager and Berends, 1974; Maskos et al., 1992). While elevations in *m*- and *o*-tyrosine concentrations were previously perceived to simply be a biological marker of reactive oxygen species, there is emerging evidence from bacterial, plant, and mammalian studies suggesting that these atypical isomers of tyrosine are actually mediators of oxidative stress. This represents a novel mechanism by which oxidative stress may disrupt cell structure and function. It is therefore conceivable that the cellular defenses against the accumulation and adverse effects of *m*- and *o*-tyrosine are two-fold: (1) the reduction of reactive oxygen species and other free radicals via classical anti-oxidative stress mechanisms (*e.g.* superoxide dismutase, glutathione, reactive oxygen species scavengers, etc.), and (2) the elimination of the abnormal tyrosine isomer pool via the activation of metabolic and degradation pathways. Only when both defenses are impaired would pathogenic phenotypes be observed. Thus previously unheralded metabolic pathways may prove to be a missing link in specifying the effects of free radicals in aging and disease progression.

Here we review the formation of these abnormal tyrosine isomers as well as their elevation in disease states. Additionally we will summarize the literature revealing their toxicity to cells and tissues and the mechanism(s) by which this may occur. Finally, we will propose future directions that may help elucidate their role in aging and disease as well as the physiologic and cellular defenses against their accumulation by excretion or metabolic degradation.

2. Formation of abnormal tyrosine isomers, *meta*- and *ortho*-tyrosine by oxidative stress

Apart from the optical isomers D- and L-tyrosine, there exist three structural isomers of tyrosine – *para*-, *meta*-, and *ortho*-tyrosine – that differ according to the position of their hydroxyl group on the benzyl side chain (Fig. 1). The *para* isoform is the one depicted in biochemistry textbooks and the major isoform involved in metabolism and protein synthesis in the cell. While enzymatic pathways have been identified for the synthesis of *m*-tyrosine in certain species of bacteria (Zhang et al., 2011) and plants (Huang et al., 2012; Muller and Schutte, 1967), in animals the enzymatic oxidation of phenylalanine by phenylalanine hydroxylase appears to occur exclusively on carbon 4, which produces *p*-tyrosine (Halliwell and Whiteman, 2004; Kaur and Halliwell, 1994). However, under conditions of oxidative stress when levels of free radicals are elevated or following exposure to ionizing radiation, non-enzymatic hydroxylation of phenylalanine may occur, resulting in the formation of the abnormal tyrosine isomers *m*- and *o*-tyrosine in addition to *p*-tyrosine (Fig. 2) (Davies et al., 1999; Mager and Berends, 1974; Maskos et al., 1992).

As depicted by Fig. 2, the formation of these tyrosine isomers by hydroxyl radical oxidation of phenylalanine involves a two-step process in which the hydroxyl radical first attacks the phenyl ring as an addition reaction to produce the highly reactive hydroxyphenylalanine radical intermediate. Next, this intermediate product quickly undergoes a secondary reaction to generate the stable tyrosine isomer by one of three mechanisms: (1) *abstraction,* in which a second hydroxyl radical or other free radical can steal the hydrogen atom bonded to the hydroxylated carbon of the phenyl ring and, in the reaction with another hydroxyl radical, release water (Mujika et al., 2013; Wang et al., 1993); (2) *oxygenation,* in which the radical intermediate reacts with oxygen with the subsequent release of a hydroperoxyl radical (Maleknia and Downard, 2001); or (3) *disproportionation,* in which two radical intermediates react with one another producing one phenylalanine molecule, one tyrosine isomer, and water (Kaur and Halliwell, 1994; Solar, 1985). In addition to reactions with hydroxyl radical, the non-enzymatic hydroxylation of phenylalanine may also