Toxicity of meta-Tyrosine

Subjects: Biology

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meta-Tyrosine (*m*-Tyr) is a non-proteinogenic isomer of *p*-tyrosine (Tyr) and is an antimetabolite of proteinogenic amino acid phenylalanine (Phe). This compound can be found in animal and plant cells.

allelochemical non-proteinogenic amino acid fescue phenylalanine antimetabolite

1. Introduction

Twenty canonical amino acids (AAs) are the base of the proteins structure in living organisms. Besides them, numerous non-proteinogenic amino acids (NPAAs) are produced in plants [1]. Some of the NPAAs are described as antimetabolites, analogs of proteinogenic AAs, and serve as toxins. The negative effect of a specific NPAA may be removed by the application of its proteinogenic analog.

2. Tyrosine Structural Isomers: *meta-, ortho-, para-Tyr*

Depending on the location of a hydroxyl group in the benzyl ring, three structural Tyr isomers are described: (i) *para*-(*p*-Tyr), which is the most common product of metabolic reactions integrated into proteins; and (ii) *meta*-(*m*-Tyr) and (iii) *ortho*-(*o*-Tyr), which are both products of the oxidation of Phe, known also as markers of oxidative stress [2] (**Figure 1**). The *o*-Tyr has been proven to have a deteriorative effect in animal cells [3], as well as in plants.

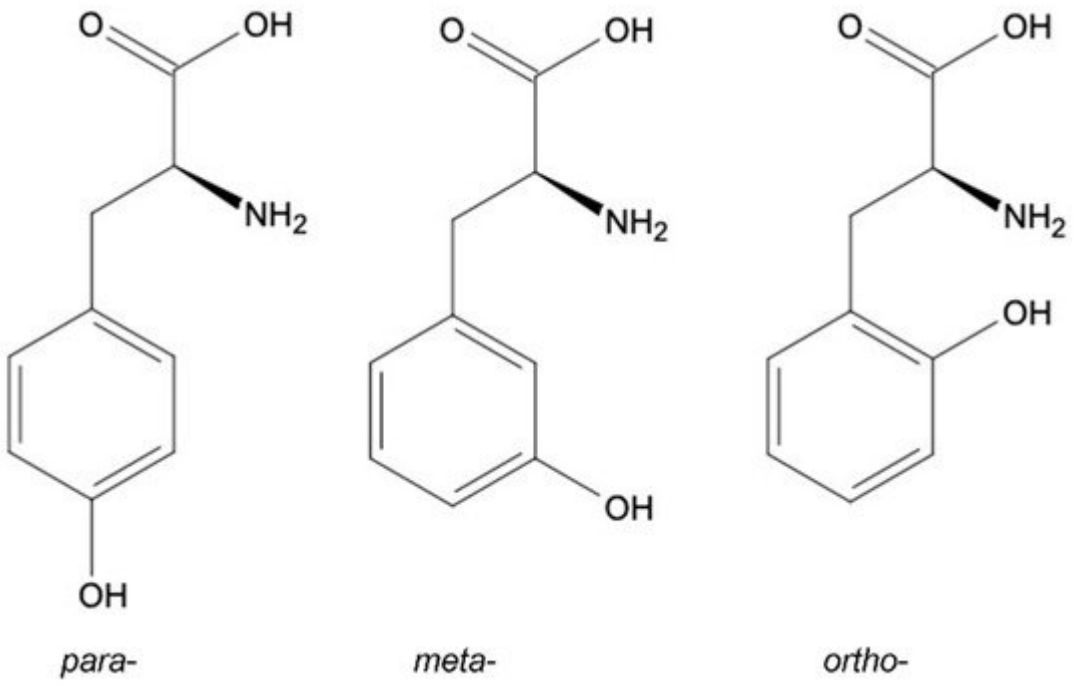

Figure 1. Structural isomers of Tyr: *para*-Tyr, *meta*-Tyr, *ortho*-Tyr.

3. Fescue as the Biological Source of *m-Tyr*

The genus of fescue (*Festuca* L.) includes about 450 species around the world[4]. Of agronomical importance are mainly fine leaf fescues (*Festuca rubra* L. spp. rubra, *Festuca rubra* L. spp. *trichophylla* Gaud., and spp. *littoralis* (Meyer) Auquiz), fescues forming clumps (*Festuca rubra* L. spp. commutata Gaud.), and sheep fescue (*Festuca ovina* L.)[5]. Fescue grasslands do not contain other species characteristic for grassland habitats e.g., clover (*Trifolium* L. sp.), dandelion (*Taraxacum* F.H. Wigg. sp.), or daisies (*Bellis* L. sp.). This is because most of the fescues produce allelopathic compounds that inhibit the growth and development of neighboring plants. At the beginning of the 21st century, 78 species of fescue were examined, among which the seven most strongly limiting the weed infestation in field conditions were selected [5]. Further laboratory analyses have shown that the allelopathic potential of fescues corresponds to their root exudates. The main fescues' root exudates component is *m*-Tyr, and the highest content of *m*-Tyr was recorded in the exudates of *F. rubra* spp. *commutata* and *F. rubra* spp. *rubra* [5]. The content of *m*-Tyr in the roots of fescue seedlings (about 6500 pmol mg^{-1} FW) was about 10 times higher than in leaves (590 pmol mg^{-1} FW). In dry seeds, *m*-Tyr was present at a much lower concentration, about 24 pmol mg^{-1} FW [6]. In fescues, epidermal cells of the root apex are responsible for the synthesis and release of exudates containing *m*-Tyr into the environment [5]. Fescues tolerate the presence of *m*-Tyr in the tissues possibly through its accumulation in intracellular or intercellular spaces [7]. The half-life of *m*-Tyr is rather short; it is estimated that, in filter paper bioassays, the *m*-Tyr half-life is less than 2 days and, in soil bioassays, less than 24 h [8]. *m*-Tyr was detected in the donkey-tail spurge (*Euphorbia myrsinites* L.), but this plant does not exudate this NPAA into the environment [6]. As a secondary metabolite, *m*-Tyr is produced by some bacteria and may be a component of antibiotics, for example, pactamycin [9].

4. Mode of action of *m-Tyr*

The direct mode of action linked to *m*-Tyr toxicity is its incorporation into the proteins [9]. In *Escherichia coli* incorporation occurs through the binding of *m*-Tyr to the $tRNA^{Phe}$ [10]. As was shown for bacteria and human cells the cytoplasmic or mitochondrial aminoacyl-tRNA synthetases are prone to catalyzing the binding of $tRNA^{Phe}$ with *m*-Tyr [11], thus Tyr isomers at higher concentration compete with Phe, for $tRNA^{Phe}$ [12]. The incorporation of *m*-Tyr into plant proteins was also demonstrated for 5-days old Arabidopsis seedlings [13].

The toxicity of *m*-Tyr might be overcome by the Phe application [14]. The mechanism of recovery effect is most probably based on the competition between Phe and *m*-Tyr [15]. *m*-Tyr toxicity is also linked to altered reactive oxygen species (ROS) metabolism including accumulation of carbonylated proteins [14][16]. Besides alteration of ROS metabolism, *m*-Tyr has an impact on reactive nitrogen species (RNS) content [16][17] .

In humans, elevated concentration of this Tyr isomer occurs in neurodegenerative diseases and diseases associated with oxidative stress and/or ageing: diabetes, artherosclerosis and others [18]. Moreover, *m*-Tyr can play a significant role in the cancer cells in animals. The concomitant tumor resistance is the phenomenon of inhibition of secondary tumor implants or metastasis development in hosts, that already are affected by the primary tumor [19]. *m*-Tyr and *o*-Tyr were found to be a factor leading to that resistance as they were discovered in the serum of tumor-bearing mice (*Mus musculus*). Administration of these NPAAs inhibited the growth of tumors in the murine models of cancer [20]. As was discussed, while secondary tumors are inhibited by circulating *m*-Tyr, the primary tumor microenvironment is protected by an accumulation of AA with counteracting properties (i.e. Phe) [21]. The primary tumor affected ROS generation resulting in the increased *m*-Tyr and *o*-Tyr content [20]. This effect was observed in different human tumors type (prostate tumor, lung anaplastic, and nasopharyngeal carcinoma), where the application of *m*-Tyr led to inhibition of cancer proliferation [22]. The treatment of cancer cells with *m*-Tyr induced the autophagy, however, the application of Phe reversed the toxic effect of *m*-Tyr on secondary cancer growth [20][22]. Studies on the key role of non-proteinogenic Tyr isomers in the mechanism of concomitant tumor resistance have shown an antiproliferative and anti-metastaic effect of *m*-Tyr [20][21][22]. Moreover, *m*-Tyr can stop the growth of cells from tumor fragments that could have remained post surgery.

Phe might overcome the toxic effect of *m*-Tyr. Increased Phe level may be achieved by the inhibition of the activity of Phe hydroxylase (the enzyme responsible for Phe catabolism). On the other hand, the degradation of Tyr isomers may occur by the higher activity of tyrosine aminotransferase (Tyr-AT) – first enzyme in the Tyr catabolism pathway [18].

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