FREE RADICAL RESEARCH
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ORIGINAL ARTICLE

Hydroxyl radical scavenging activity of melatonin and its related indolamines

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ABSTRACT

The hydroxyl radical (•OH) scavenging activities of Melatonin, an endogenously produced neurohormone and its related indolamines like *N*-acetyl tryptophan (NAT) and *N*-acetyl serotonin (NAS) have been investigated using density functional theory. The mechanism involves 4 steps: initial radical addition to position-3 of the indole ring, keto-amine to enol-imine tautomerization, cyclisation, and finally, addition of a second •OH leading to a cyclic end product. Incorporation of an explicit water molecule in tautomerization step leads to a significant reduction in the barrier of this step, so that the subsequent cyclisation step becomes rate-limiting. In agreement with the very high reactivity of •OH, the initial and final addition of •OH to indolamine are found to be barrierless. Radical adduct formed in the initial step was found to be very stable due to the extensive conjugation present in the substrate. Our calculations show that melatonin is the most effective radical scavenger among the three molecules chosen. NAS was found to exhibit antiradical property comparable to that of melatonin. In contrast to the general observation of reduced antioxidant activity of tryptophan, a non-natural derivative of tryptophan used here (NAT) is found to have good radical scavenging activity. This work further implies that non-natural derivatives of indolamines might as well be useful in the detoxification of free radicals as they exhibit almost comparable antioxidant efficiency as that of melatonin.

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Introduction

Oxidative stress due to the free radical induced cellular damage is believed to be the probable reason for a number of adverse health conditions; especially chronic diseases such as diabetes, neurodegenerative and cardiovascular diseases [1–3]. Consequently, significant research efforts have been devoted for discovering biomolecules with an effective antioxidant profile to cure these adverse conditions. Melatonin (*N*-acetyl-5-methoxytryptamine), a neurohormone secreted by pineal gland is one such biomolecule that has received substantial consideration due to its existence in every cellular components and versatile properties [4,5]. Melatonin acts as the mediator of many physiological functions related to circadian rhythm, retinal physiology, sleep–wake cycle, neuroendocrine and immune functions [6] due to its ability to easily cross bio-physiologic barriers and quickly transport into the cells, making it a potent antioxidant [7,8]. An electron rich aromatic system and the amphiphilicity of the compound arising from *O*-methyl and *N*-acetyl residues are supposed to be the molecular bases for the antioxidant properties [9]. Under the condition of severe oxidative stress, melatonin is found to be metabolised *via* enzymatic degradation or free radical interactive processes. [10] These metabolites include hydroxylated melatonin metabolites (6-hydroxymelatonin, 2-hydroxymelatonin, and 4-hydroxymelatonin), *N*1-acetyl-*N*2-formyl-5-methoxykynuramine (AFMK), *N*-acetyl-5-methoxyknuramine (AMK) and cyclic 3-hydroxy melatonin, which also fight against free radicals. [11] Thus, melatonin can be considered to be a broad spectrum antioxidant whose never ending action is associated with its degradation pathway and formed metabolites. [10,11]. Interestingly, melatonin also helps stimulate enzymatic antioxidants like superoxide dismutase, glutathione reductase and catalase [12]. Tryptophan, the precursor of melatonin can also extend the defence mechanism against free radicals with its natural and non-natural derivatives [13,14]. For

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Supplemental data for this article can be accessed here.