Life Sciences 148 (2016) 305–312

Contents lists available at ScienceDirect

Life Sciences

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

Review

Melatonin and caffeic acid phenethyl ester in the regulation of mitochondrial function and apoptosis: The basis for future medical approaches

Haci Kemal Erdemli [a,*], Sumeyya Akyol [b,c], Ferah Armutcu [d], Mehmet Akif Gulec [e], Metin Canbal [f], Omer Akyol [c,g]

[a] Department of Biochemistry Laboratory, Corum Training and Research Hospital, Corum, Turkey
[b] Department of Medical Biology, Faculty of Medicine, Turgut Ozal University, Ankara, Turkey
[c] Vascular & Medicinal Research, Wafic Said Molecular Cardiology Research Laboratories, Texas Heart Institute, Houston, TX, United States
[d] Department of Medical Biochemistry, Cerrahpasa Medical Faculty, Istanbul University, Istanbul, Turkey
[e] Department of Medical Biochemistry, Faculty of Medicine, Turgut Ozal University, Ankara, Turkey
[f] Department of Family Medicine, Faculty of Medicine, Turgut Ozal University, Ankara, Turkey
[g] Department of Medical Biochemistry, Faculty of Medicine, Hacettepe University, Ankara, Turkey

ARTICLE INFO

Article history:
Received 21 September 2015
Received in revised form 12 January 2016
Accepted 13 January 2016
Available online 16 January 2016

Keywords:
Melatonin
Caffeic acid phenethyl ester
Mitochondria
Apoptosis
Antioxidant

ABSTRACT

The aim of this review article is to summarize and compare the effects of melatonin and caffeic acid phenethyl ester (CAPE) on the relationship between mitochondrial functioning and apoptosis. References in this article were selected with an approach based on a comprehensive literature review by using MEDLINE/PubMed and Google Scholar databases which were scanned in the last six months without any restrictions. For each database, the review terms used are 'melatonin', 'caffeic acid phenethyl ester, both together and associated with other key words such as apoptosis and mitochondria. Evidential mitochondrial molecular backgrounds for diseases make these two molecule competitors, since both of them use the same pathways to cope with fundamentals of the diseases such as nuclear factor κ-light-chain-enhancer of activated B (NF-κB inhibition, induction of mitochondrial apoptosis in cancer cells, free radical scavenging effects, and antioxidant activities. The data reviewed in this paper provide a useful background for the understanding of some molecular details of melatonin and CAPE on several medical situation and diseases. Mutual usage of these two tremendous molecules might have a capacity to open new therapeutic approaches in near future.

Contents

* Corresponding author at: Corum Training and Research Hospital, Department of Biochemistry Laboratory, Bahcelievler Mahallesi Camlik Caddesi No: 2, Corum, Turkey.
E-mail address: hkemal@hotmail.com (H.K. Erdemli).

http://dx.doi.org/10.1016/j.lfs.2016.01.026
0024-3205/

1. Introduction

Melatonin (N-acetyl 5-methoxytryptamine) is the main hormone (Fig. 1) secreted from the pineal gland; however, it has been identified in extrapineal organs and tissues such as gastrointestinal tract, retina, lens, skin, testes, lymphocytes and hematopoietic cells. Melatonin is a highly lipophilic molecule that crosses cell membranes and easily reaches high concentrations at subcellular compartments including mitochondria [1,2]. Being a well-known antioxidant and free radical scavenger, melatonin shows protective effects against oxidative damage in several tissues including heart, kidney, liver, and brain [3]. Furthermore, melatonin efficiently interacts (direct scavenging of radicals) with diverse reactive oxygen and nitrogen species (ROS and RNS), up-regulates antioxidant enzymes, down-regulates pro-oxidant enzymes, and preserves mitochondrial homeostasis. A summary of melatonin's cellular antioxidant effects is presented in Table 1 [4,5]. Caffeic acid phenethyl ester (CAPE) (Fig. 1) is among important compounds found in propolis that shows antioxidant, anti-inflammatory, antiproliferative, antitumor, and immunomodulatory effects [6,7]. It has been utilized in order to prevent oxidative stress (OS)-based deterioration in cells/tissues/organs in both cell culture and experimental models. CAPE was shown to completely prevent production of ROS in human neutrophils and in the xanthine/xanthine oxidase (XO) systems at 10 μM concentration by its competent antioxidant capacity [8]. Furthermore, CAPE has a regulatory effect towards antioxidant enzyme activities such as catalase, superoxide dismutase (SOD), and glutathione peroxidase (GPx) [9]. In this study, we aimed to critically compare the potential protective properties of melatonin and CAPE against several diseases in which OS and inflammation are accused to be pathogenic factors in the pathophysiology of disease. Moreover, since mitochondria are the main cellular organelle and mitochondria-centered critical mechanisms such as apoptosis are the most important factors in the progression of various diseases, we aimed to present the clues and prove connections between mitochondrial mechanisms and these two molecules, melatonin and CAPE. Therefore, we searched for studies published in English in the last two decades by using the MEDLINE/PubMed and Google Scholar databases. For each database, the review terms used are 'melatonin', 'caffeic acid phenethyl ester', both together and associated with other key words such as apoptosis and mitochondria. This article systematically reviews and summarizes relationship between mitochondrial functioning, apoptosis and CAPE in comparison with melatonin.

2. General information on mitochondrial apoptosis

Apoptosis (programmed cell death) is well-described by different morphological features and energy-dependent biochemical mechanisms. It is a crucial step of several biological activities including cell cycle, tissue homeostasis, embryonic development, functioning of the immune system, and chemical-induced cell death. Incompatible apoptosis is a reason in many pathological situations including ischemic injury, autoimmune disorders, various cancers, and neurodegenerative diseases [10,11]. On the other hand, cell death and neurodegenerative conditions have been linked to OS and imbalance between generation of oxidants and antioxidant defenses. Apoptosis is characterized by caspase-dependent cleavage of several cellular substrates that leads to efficient detection, packaging and elimination of the targeted cells from surrounding environment [12]. Apoptosis is mainly regulated by two major pathways; *i*, the extrinsic pathway, in which receptors are located at plasma membrane, start initial process of apoptosis, and *ii*, the intrinsic pathway, where the key processes occur in mitochondria (Fig. 2). Activation of caspases, cysteine-dependent aspartate-specific proteases, plays an important role in both intrinsic and extrinsic pathways [13,14]. Moreover, several researchers have suggested that OS is also a pivotal player, and as signaling molecules ROS is related to apoptosis [15]. Apoptosis can be inhibited or delayed by antioxidants and promoted by ROS production in various cells types. In the recent studies, melatonin, which is a powerful antioxidant, has been proposed as a drug in the treatment of many diseases including cancer and mitochondrial pathologies [16,17].

3. Therapeutic features and applications of melatonin

Melatonin is derived from tryptophan amino acid and a member of indoleamine hormones. Indoleamines have protective effects on aging, Parkinson's (PD) and Alzheimer's disease (AD), sepsis and ischemia/reperfusion (I/R) injury [1]. The common properties of these disorders are dysfunction in apoptosis and cell cycle. Thus, the problems, which lead improper apoptotic processes, can exacerbate cancer, neurodegenerative disorders and ischemic conditions [15,17]. Mitochondrial diseases are generally inherited illness that can be present at birth or develop later in life, but adult-onset forms are becoming more and more common. They primarily affect brain, heart and muscle in varying levels of severity and look like any number of better known diseases; Autism, AD and PD, muscular dystrophy and chronic fatigue [18]. The damage in the brain, heart, skeletal muscles, liver, kidney, endocrine and respiratory systems show important health problems. Moreover, recent evidences suggest that mitochondria may perform as key mediators in the onset and progression of some types of neurodegeneration [19]. Although the etiology and pathogenesis of many neurodegenerative diseases remain largely unknown; frequently OS-mediated injury, glutamate excitotoxicity and mitochondrial dysfunction have been recognized as common pathophysiological mechanisms or interrelated processes leading to death of nerve cells. Melatonin maintains mitochondrial homeostasis, reduces ROS generation and enhances the

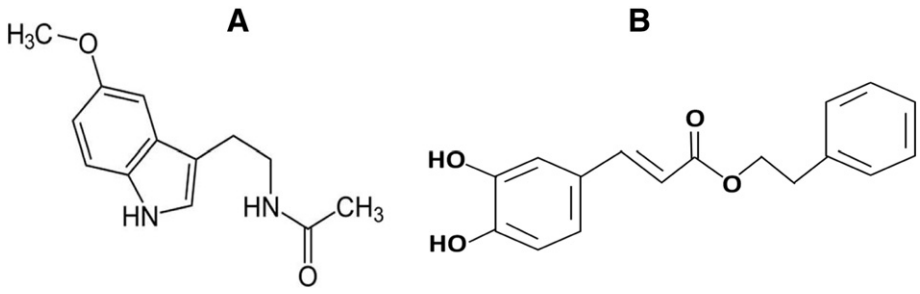

Fig. 1. The molecular structures of melatonin (A) and caffeic acid phenethyl ester (B).