Pharmacological Research 117 (2017) 252–260

Contents lists available at ScienceDirect

Pharmacological Research

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

Invited Review-pharmacology across disciplines

Melatonin as a promising agent of regulating stem cell biology and its application in disease therapy

Shuo Zhang[a], Simon Chen[c], Yuan Li[a], Yu Liu[b,*]

[a] College of Pharmacy, Harbin Medical University, Harbin 150081, Heilongjiang Province, China
[b] Department of Clinical Laboratory Diagnosis, the Fourth Affiliated Hospital of Harbin Medical University, Harbin 150001, Heilongjiang Province, China
[c] Cumming School of Medicine, University of Calgary, Calgary, Canada

ARTICLE INFO

Article history:
Received 27 October 2016
Received in revised form
22 December 2016
Accepted 22 December 2016
Available online 30 December 2016

Keyword:
Melatonin
Stem cells
Proliferation
Differentiation
Migration
Stem cell therapy

ABSTRACT

Stem cells have emerged as an important approach to repair and regenerate damaged tissues or organs and show great therapeutic potential in a variety of diseases. However, the low survival of engrafted stem cells still remains a major challenge for stem cell therapy. As a major hormone from the pineal gland, melatonin has been shown to play an important role in regulating the physiological and pathological functions of stem cells, such as promoting proliferation, migration and differentiation. Thus, melatonin combined with stem cell transplantation displayed promising application potential in neurodegenerative diseases, liver cirrhosis, wound healing, myocardial infarction, kidney ischemia injury, osteoporosis, etc. It exerts its physiological and pathological functions through its anti-oxidant, anti-inflammatory, anti-apoptosis and anti-ageing properties. Here, we summarize recent advances on exploring the biological role of melatonin in stem cells, and discuss its potential applications in stem cell-based therapy.

Contents

1. Introduction 253
   1.1. Melatonin 253
   1.2. Stem cells 253
   1.3. Melatonin receptors 253
2. The actions of melatonin on stem cells 253
   2.1. Mesenchymal stem cells (MSCs) 253
   2.2. Neural stem cells (NSCs) 255
   2.3. Hemopoietic stem cells 255
   2.4. Spermatogonial stem cells 255
   2.5. Embryonic stem cells (ESCs) 255
   2.6. Induced pluripotent stem cells (iPSCs) 255
   2.7. Cardiac stem cells (CSCs) 255
   2.8. Amniotic epithelial cells (AECs) 255
   2.9. Human dental pulp stem cells (hDPSCs) 255
   2.10. Others 255
3. Application of melatonin in stem cell-based therapy 256
   3.1. Nervous system diseases 256
   3.2. Bone diseases 256
   3.3. Brain diseases 256
   3.4. Anti-aging 256

* Corresponding author.
E-mail address: rainfall1982@163.com (Y. Liu).

http://dx.doi.org/10.1016/j.phrs.2016.12.035
1043-6618/

3.5. Kidney diseases 256
3.6. Lung diseases 256
3.7. Liver diseases 257
3.8. Intestine diseases 257
3.9. Heart diseases 257
3.10. Bladder diseases 257
3.11. Skin wound healing 257
3.12. Metabolism diseases 257
3.13. BRONJ 257
3.14. Tumor 257
4. Melatonin analogues, melatonin agonists and antagonists 258
4.1. Melatonin analogues 258
4.2. Melatonin agonist 258
4.3. Melatonin antagonist 258
5. The prospects and problems of melatonin's application 258
Conflict of interest 258
Acknowledgements 258
References 258

1. Introduction

1.1. Melatonin

Melatonin (*N*-acetyl-5-methoxytryptamine), a neurohormonal peptide initially, is produced in the pineal gland [1] (Fig. 1). It is widely detected in various locations in body, such as bone marrow, lymphocytes, the gastrointestinal tract, skin and so on [2]. Besides its well-known functions in circadian rhythms, melatonin and its derived metabolites possess antioxidant properties, such as scavenging excessive free radicals and increasing the synthesis of antioxidant enzymes in vivo and in vitro [3]. Melatonin is also distinguished for its anti-inflammatory reaction and ability to maintain biomembrane stability [4]. Additionally, melatonin has biological activities of modulating mitochondrial activity and the immune system, as well as anti-apoptotic, anti-tumor and anti-ischemic properties [5].

1.2. Stem cells

Stem cells are undifferentiated cells, which can differentiate into specialized cells under certain induction microenvironments in multicellular organisms. For example, totipotent stem cells are capable of giving rise to a fully functional organism. Pluripotent stem cells divide into virtually any tissue type, but not a functional organism. Multipotent stem cells may differentiate into a limited number of tissues [6]. Stem cell-based therapy has shown to have novel clinical implications, through cytothesis, replacement or regeneration to improve organ function. However, there are still many limitations such as poor survival, long-term stability, culture medium, scaffold materials, delivery systems, oncogenic potential and functional integration as well as technical limitation [7]. Nevertheless, stem cells have displayed promising application potential in the treatment of diseases such as liver cirrhosis [8], neuritis [9], heart disorders [10], spinal cord injuries (SCI) [11], stroke [12], Parkinson's [13] and Alzheimer's diseases [14]. Furthermore, stem cells are implicated in the development of assay systems to test new drugs *in vitro* [15].

1.3. Melatonin receptors

Several types of melatonin receptors have been identified, such as MT_1, MT_2, MT_3 (cytosolic binding sites) and the RZR/ROR family acting as nuclear receptors [16]. Among them, MT_1 and MT_2 are the most commonly and widely studied. Numerous biological functions of melatonin in mammals are mediated via activating of the G-protein-coupled MT_1 or MT_2 [17]. However, some studies also showed that the biological function of melatonin was not mediated by activation of melatonin receptors. This suggests that melatonin regulates physiological and pathological activities of various cells through two ways: melatonin receptor-dependent manner and melatonin receptor-independent manner.

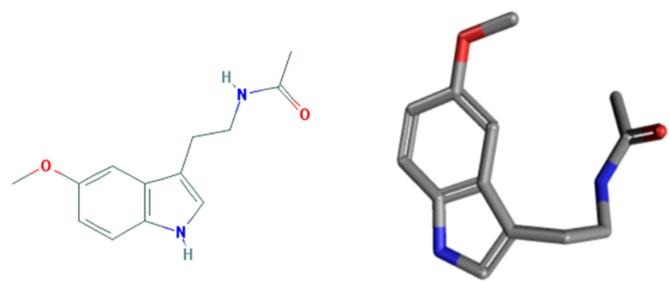

Fig. 1. The molecular and crystal structure of melatonin.

2. The actions of melatonin on stem cells

Increasing evidence show that melatonin plays a regulatory role in the viability, proliferation and differentiation of stem cells, which is supposed to have promising applications in stem cell therapy for many diseases [18]. Here we summarized the effects of melatonin in the different type of cells in the recent years.

2.1. Mesenchymal stem cells (MSCs)

Melatonin takes part in the regulation of osteogenic, adipogenic, myogenic and chondrogenic differentiation of MSCs. As recent studies illuminate, therapeutic effects of MSCs have been confirmed in animal models of acute kidney ischemia injury (AKI) [19,20], acute lung ischemia injury (ALI) [21], acute interstitial cystitis (AIC) [22], ischemia brain injury (IBI) [23], myocardial infarction (MI) [10], small bowel ischemia-reperfusion injury (SBIR) [24], osteoporosis (OP) [25], bisphosphonate-related osteonecrosis of the jaw (BRONJ)[7], central nervous system diseases [26], arthritis [27], wound healing [28] and other diseases (Fig. 2) (Table 1). Melatonin plays an important role in the control of MSCs survival, proliferation, apoptosis and differentiation by certain signaling pathways (Fig. 3). For instance, the activation of MT_2 influences Wnt/β-catenin signaling in MSCs [29] (Fig. 3). Likewise, melatonin effectively inhibited Bax/Bcl-2, activiated caspase-3 activity and phospho-p38 MAPK pathway, and promoted intracellular ROS