Life Sciences 115 (2014) 8–14

Contents lists available at ScienceDirect

Life Sciences

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

Review article

Melatonin as a proteasome inhibitor. Is there any clinical evidence?

Jerry Vriend [a,*], Russel J. Reiter [b]

[a] Department of Human Anatomy and Cell Science, University of Manitoba, Winnipeg, Manitoba, Canada
[b] Department of Cellular and Structural Biology, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA

ARTICLE INFO

Article history:
Received 15 July 2014
Accepted 27 August 2014
Available online 16 September 2014

Chemical compounds studied in this article:
Melatonin (PubChem CID: 896)
Bortezomib (PubChem CID: 387447)

Keywords:
Melatonin
Proteasome
Apoptosis
Bax
Bim
Bcl-2
Tumor suppressor p53
Nuclear factor kappa beta
Caspase 3
Caspase 9
TRAIL

ABSTRACT

Proteasome inhibitors and melatonin are both intimately involved in the regulation of major signal transduction proteins including p53, cyclin p27, transcription factor NF-κB, apoptotic factors Bax and Bim, caspase 3, caspase 9, anti-apoptotic factor Bcl-2, TRAIL, NRF2 and transcription factor beta-catenin. The fact that these factors are shared targets of the proteasome inhibitor bortezomib and melatonin suggests the working hypothesis that melatonin is a proteasome inhibitor. Supporting this hypothesis is the fact that melatonin shares with bortezomib a selective pro-apoptotic action in cancer cells. Furthermore, both bortezomib and melatonin increase the sensitivity of human glioma cells to TRAIL-induced apoptosis. Direct evidence for melatonin inhibition of the proteasome was recently found in human renal cancer cells.

We raise the issue whether melatonin should be investigated in combination with proteasome inhibitors to reduce toxicity, to reduce drug resistance, and to enhance efficacy. This may be particularly valid for hematological malignancies in which proteasome inhibitors have been shown to be useful. Further studies are necessary to determine whether the actions of melatonin on cellular signaling pathways are due to a direct inhibitory effect on the catalytic core of the proteasome, due to an inhibitory action on the regulatory particle of the proteasome, or due to an indirect effect of melatonin on phosphorylation of signal transducing factors.

Contents

* Corresponding author at: Department of Human Anatomy and Cell Science, University of Manitoba, 745 Bannatyne Avenue, Winnipeg R3E 0W3, Manitoba, Canada. Tel.: +1 204 789 3732, +1 204 668 2871.
E-mail address: Vriend@ms.umanitoba.ca (J. Vriend).

http://dx.doi.org/10.1016/j.lfs.2014.08.024
0024-3205/

Introduction

Some of the major proteins of significance in cancer susceptibility include the tumor suppressor factor, p53, cell cycle regulator, p27, transcription factor NF-κB, anti-apoptotic factor Bcl-2, and the pro-apoptotic factor Bax. Cellular levels of these proteins are controlled by the ubiquitin–proteasome system and are targets of the proteasome inhibitor, bortezomib (Chen et al., 2011; Fuchs, 2013). Each of these proteins has also been reported to be influenced by the naturally-occurring indole, melatonin (Fig. 1). The increasing number of proteins reported as regulated by both the proteasome and by melatonin suggests the hypothesis that melatonin acts as an inhibitor of a component of the ubiquitin–proteasome system (Vriend and Reiter, 2014). Herein, we review the signal transduction proteins whose levels are modulated both by the ubiquitin–proteasome system and by melatonin, and we discuss mechanisms by which melatonin could interact with the ubiquitin–proteasome system in cancer cells. The use of proteasome inhibitors in treating some hematological disorders and cancers raises the question of whether melatonin should be added to drug regimens used to treat specific malignancies that are sensitive to proteasome inhibitors.

Shared targets for proteasome inhibitors and melatonin

Several major targets of proteasome inhibitors were identified followed by the approval of bortezomib by the US Food and Drug Administration in 2004 for treatment of multiple myeloma. The effects of proteasome inhibitors on signal transduction proteins have been regularly reviewed (e.g. Adams et al., 1999; Chen et al., 2011; Crawford et al., 2011; Kisselev et al., 2013; Wu and Shi, 2013). Thus, treatment with proteasome inhibitors increases tumor suppressor protein p53, increases the cell cycle regulator p27, inhibits levels of the transcription factors NF-κB and beta-catenin, enhances apoptosis, inhibits angiogenesis and inhibits DNA repair. Herein, we provide documentation that melatonin administration influences the activity of the major targets of the proteasome inhibitor, bortezomib.

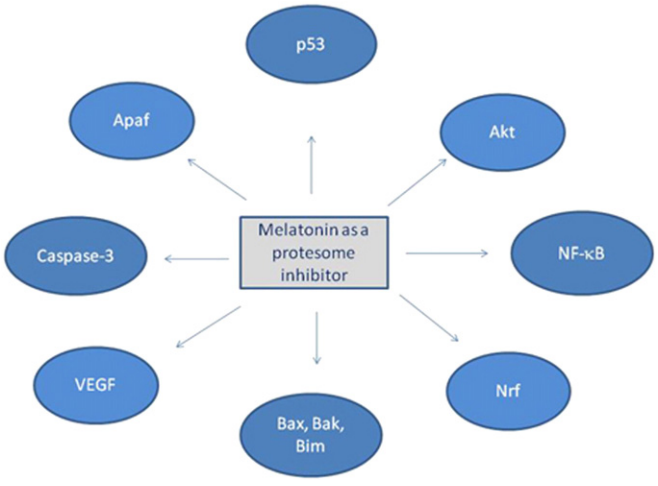

Fig. 1. Is melatonin a proteasome inhibitor? p53 — tumor suppressor protein; Akt — protein kinase B; NF-κB — nuclear factor kappa beta, a transcription factor; Nrf2 — nuclear factor-like 2, a transcription factor related to response to oxidative stress; Bax — Bcl-2-associated X protein; Bim — a protein that regulates apoptosis; Bak — another apoptotic factor of the Bcl-2 family; VEGF — vascular endothelial growth factor; caspase 3, a protein mediator of apoptosis; and Apaf — apoptosis protease activating factor, a component of the apoptosome.

NF-κB

NF-κB as a transcription factor stimulates the expression of a number of genes related to oxidative stress, the immune response, cytokine production and apoptosis (Crawford et al., 2011). It is regulated in a complex manner by the ubiquitin–proteasome system. Degradation of the NF-κB inhibitor, IκK, by the proteasome results in activation of NF-κB (Traenckner et al., 1994; Chen, 2005; Gilmore, 2006; Brasier, 2006; Perkins, 2007; Skaug et al., 2009). The proteasome inhibitor bortezomib is considered an inhibitor of NF-κB (Wu and Shi, 2013; Traenckner et al., 1994) through its effect on IκK. This mechanism is complicated, however, by the fact that degradation of NF-κB itself is regulated by the proteasome and that NF-κB can be activated by more than one signaling pathway, the canonical pathway and the non-canonical pathway (Fuchs, 2013). Furthermore, a second major factor regulating the activity of NF-κB is phosphorylation (Balistreri el al., 2013). Baldwin (2001) has made the case that inhibition of NF-κB is clinically useful in selected cancers, including lymphomas and leukemias, through an effect on apoptosis. The use of bortezomib in multiple myeloma therapy is based partly on its effects on NF-κB (Fuchs, 2013) (Fig. 2). More recently, Wu and Shi (2013) have reviewed developments regarding the use of proteasome inhibitors which suppress various types of cancer through their effect on NF-κB.

There are many reports that melatonin inhibits NF-κB activity (Natarajan et al., 1995; Chuang et al., 1996; Gilad et al., 1998; Bruck et al., 2004; Li et al., 2005; Huang et al., 2008; Jung et al., 2009; Choi et al., 2011; Bekyarova et al., 2012; Qin et al., 2012; Shi et al., 2012; Min et al., 2012) These reports would be consistent with the view that

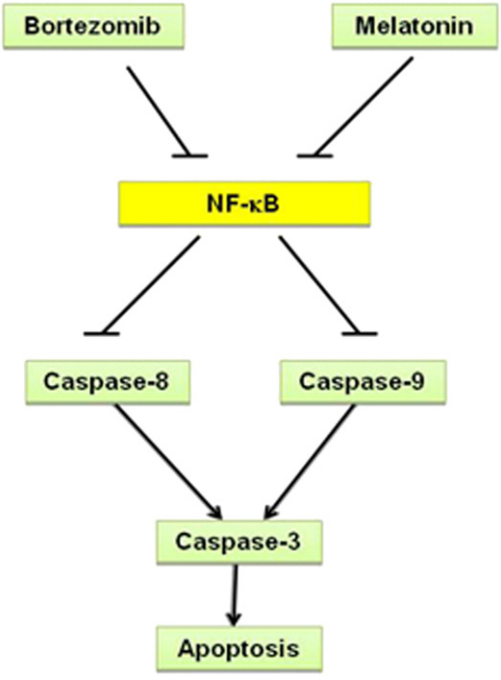

Fig. 2. Role of NF-κB in bortezomib and melatonin-induced apoptosis. Both bortezomib and melatonin inhibit NF-κB. Inhibiting NF-κB will increase apoptosis by removing an inhibitory effect on the caspase group of enzymes.