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Improvement of oxidative stress and immunity by melatonin: An age dependent study in golden hamster

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ABSTRACT

Reactive oxygen species (ROS) have been proposed to play an important role in balancing the pro- and anti-oxidant homeostasis during aging. Melatonin has been suggested as an effective free radical scavenger that might have a role during the process of aging. We observed, that melatonin administration (25 μg/100 g body weight for 30 days) significantly augments the activity of anti-oxidative enzymes like superoxide dismutase (SOD), catalase and glutathione peroxidase (GPx) in the plasma, spleen and bone marrow (BM) of young (6 weeks), adult (30 weeks) and old aged (2.5 years) male golden hamster, *Mesocricetus auratus*. A sharp decline in generation of ROS was observed in peripheral blood mononuclear cells (PBMC) and splenocytes upon melatonin administration in different age group of hamsters. Reduction in the level of thiobarbituric acid-reactive substances (TBARS) and total nitrite and nitrate concentration as metabolites and indicators of nitric oxide (NO) in plasma, spleen and BM were observed along with night time (22:00 h) melatonin concentration in different age group of hamsters after administration of melatonin and compared to the control group (treated with 0.9% saline). General immune parameters like proliferation of splenocytes, PBMC and colony forming ability of GM-CFU were observed following melatonin treatment in different age group, although it was low only in aged hamsters compared to the young and adult. Our data indicates that the age related increase of oxidative load and simultaneously augments the general immunity in aged hamsters.

1. Introduction

Aging is a complex process affecting a wide variety of physiological functions, including the development and maintenance of the peripheral immune system (Miller, 1991). The oxidative theory of aging by Harman (1956) states that reactive oxygen species (ROS) and nitrogen species (RNS) cause random damage to cells, which includes impaired physiological functions and increased incidence of diseases as the age progresses leading to mortality. ROS and RNS both induce oxidative stress during several physiological conditions like inflammation, and are responsible for increased oxidative load with advancing age (Drew and Leeuwenburgh, 2002). The nitrosative stress due to interaction between nitrosants and oxidants may produce products that are more toxic than either reactant alone causing cellular injury, predominate oxidative damage (Eu et al., 2000; Stamler and Hausladen, 1998). At the cellular level, nitric oxide (NO) has been widely implicated in nitrosative stress which is linked to inhibition of cell growth and apoptosis (Marshall et al., 2000). The detection of nitrotyrosine (NO_2-Tyr) formation in various tissue following inflammation, and during the process of aging is recognized as peroxynitrite-triggered mechanism of nitrosative injury (Beal, 2002; Bian and Murad, 2001; Drew and Leeuwenburgh, 2002; Levrand et al., 2005). Oxidative stress may also result in wide varieties of diseases and neurodegenerative disorders (Pacher and Szabo, 2008).

Decline in the production of several hormones including melatonin has been reported (Reiter et al., 1981) to play a key regulatory role in aging and senescence (Liu and Wang, 2002; Pierpaoli and Regelson, 1992) by preventing the T lymphocyte mediated immune responses (Miller, 1995). Melatonin is known for immunomodulation (Ahmad and Haldar, 2010) and reflects a general immunoenhancing property in many animal species including human (Nelson, 2004). Numbers of studies suggest that pinealectomy induces various pathological changes resembling senescence and could be reversed by the administration of pineal extract or melatonin. The mechanism of action of melatonin in immune-enhancement needs to be elucidated.

Though, the direct free radical scavenging capacity (Tan et al., 1993) and indirect antioxidant stimulatory property of melatonin have been reported in number of studies for improving metabolic

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function (Reiter et al., 2000; Rodriguez et al., 2004). To date, the age related protective effect of melatonin in immune function and oxidative stress in terms of ROS/RNS generation is lacking. We therefore explored the relationship between the age dependent melatonin secretion and modulation of immune responses along with oxidative stress in different age group of hamster under ambient condition. We also explored the protective effect of exogenous melatonin against age induced oxidative injury by accessing ROS generation, lymphocyte proliferation and colony forming ability of granulocyte macrophages (GM-CFU) in different age group of hamsters.

2. Methods

2.1. Animals

Golden hamsters (outbred strain) were procured from Central Drug Research Institute (CDRI), Lucknow, India and colony was developed and maintained in animal house facility. Hamsters were kept in a room having temperature 25 ± 2 °C with alternative light/dark cycle (12 h light, 12 h dark; i.e. lights on 07:00–19:00 h) in order to maintain the photoperiod. Animals were maintained in polypropylene cages

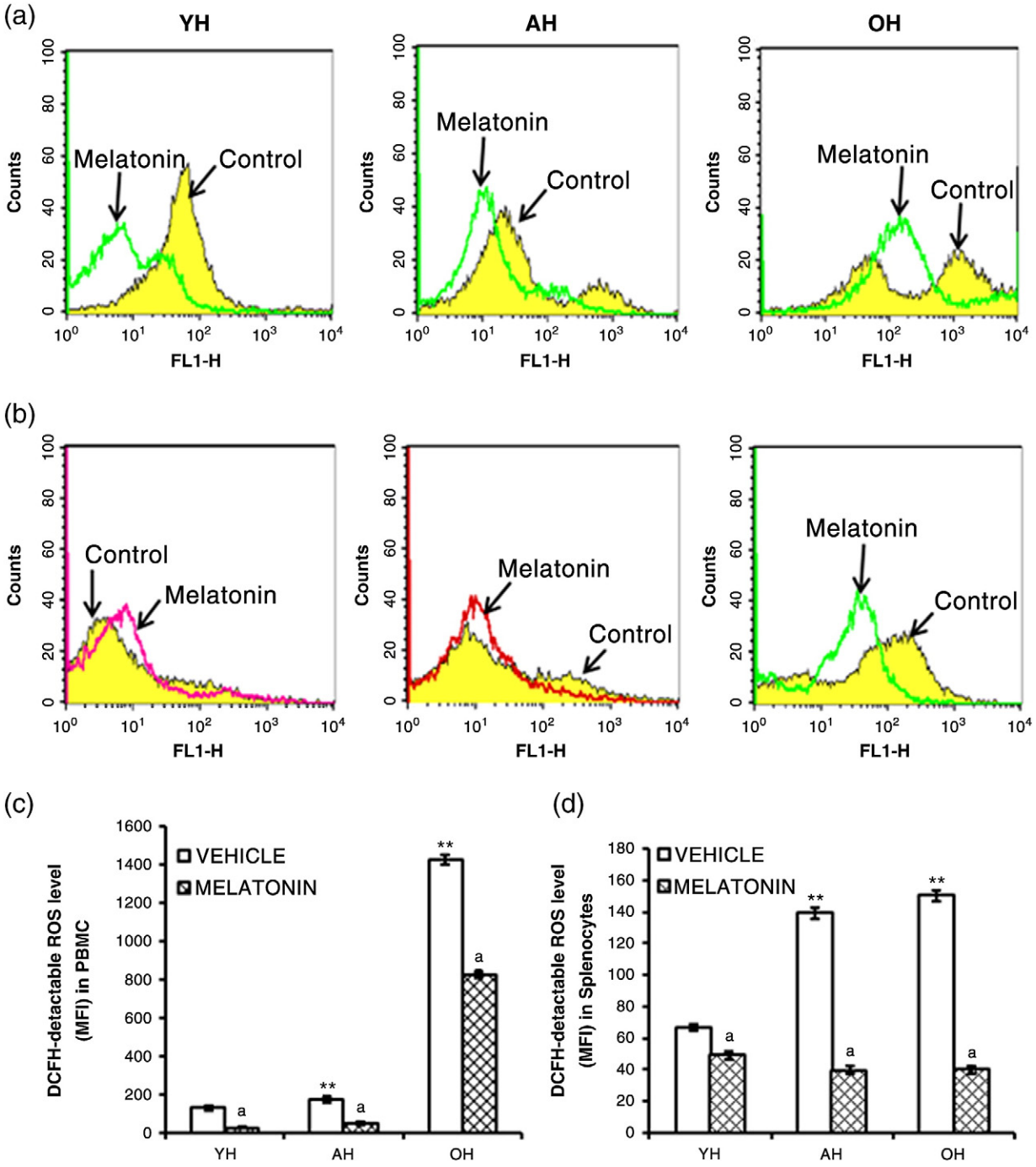

Fig. 1. Flow cytometric analysis with age and melatonin administration showing ROS generation in (a) PBMC and (b) splenocytes. Results are expressed as representative histograms showing DCFH-detectable ROS level (MFI) in (c) PBMC and (d) splenocytes. Values are expressed as MFI ± SD, N = 7. **p<0.01 young (YH) vs adult (AH) and old (OH) hamsters *M. auratus*; ap<0.01 vehicle vs melatonin treated hamster.