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Research Report

Dietary melatonin attenuates age-related changes in morphology and in levels of key proteins in globus pallidus of mouse brain

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ABSTRACT

The ability of melatonin treatment of aged animals to partially restore the pattern of gene expression characterizing the younger animal has been frequently reported. The current study examines the effect of melatonin upon age-related changes of some key proteins relevant to the aging process. Male B6C3F1 mice, aged 5.5 months and 23.4 months were used as a model for aging and half of each group received a diet supplemented with 40-ppm (w/w) melatonin for 9.3 weeks. Protein components of the globus pallidus were studied including glial fibrillary acidic protein (GFAP), NF-κB, protein disulfide isomerase (PDI), and Nissl staining. Some age-related changes were in an upward direction (GFAP and NF-κB), while others were depressed with age (PDI and intensity of Nissl staining). However, in either case, melatonin treatment of aged mice generally altered these parameters so that they came to more closely resemble the levels found in younger animals. The extent of this reversal to a more youthful profile, ranged from complete (for NF-κB) to very minor (for Nissl staining and PDI). Overall, these findings are in accord with prior data on the effect of melatonin on cortical gene expression and confirm the value of melatonin as a means of retarding events associated with senescence.

1. Introduction

Aging involves a series of multifaceted and complex degradation processes that is to gradually impair cellular and ultimately organismic efficiency. In the nervous system, these include behavioral, and neuroendocrine changes, leading to progressive loss of ability to adapt effectively to the environment, and increased susceptibility to disease. In the

Abbreviations: GFAP, glial fibrillary acidic protein; PDI, protein disulfide isomerase

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aging brain, increased neuroinflammation is evidenced by higher steady-state levels of inflammatory cytokines and decreases in anti-inflammatory molecules (Sparkman and Johnson, 2008). Elevated inflammatory responses in the aged brain can lead to increased neuronal death (Finch and Morgan, 2007; Marchalant et al., 2008) and this may form a platform enabling the progression of neurodegenerative disease (Teeling and Perry, 2009).

Melatonin (*N*-acetyl-5-methoxytryptamine) is an indole neuroendocrine hormone secreted by the pineal gland. It was first isolated from bovine pineal gland and characterized by Lerner et al. (1958) but it is meanwhile known to be also synthesized in various other organs, tissues, and cells (Pandi-Perumal et al., 2006; Hardeland, 2008). It is a multifunctional signaling molecule acting via G-protein-coupled receptors that has a variety of important functions (Hardeland et al., 2011). In addition to regulation of circadian signaling, melatonin is a powerful antioxidant and anti-inflammatory agent (Bondy and Sharman, 2010). There is evidence that melatonin has value in the treatment of a range of neurological disorders including age-associated neurodegenerative conditions, notably Alzheimer's and Parkinson's diseases (Rosales-Corral et al., 2012, Singhal et al., 2012).

The amphiphilic nature of melatonin allows it to pass readily through biological membranes (Bonnefont-Rousselot and Collin, 2010). Levels of melatonin in plasma and in brain, decline markedly with senescence (Lahiri et al., 2004). However, application of exogenous melatonin by way of the diet can increase cortical levels of free unconjugated melatonin (Lahiri et al., 2004). This may extend life expectancy, postpone aging, reducing the incidence of age-related diseases (Bondy and Sharman, 2010; Tan et al., 2010). Melatonin treatment can partially reverse many of the increases in expression of genes related to inflammation that take place with aging (Sharman et al., 2007). This leads to a more youthful response to an inflammatory challenge (Perreau et al., 2007). This influence on gene expression may underlie the many reported attributes of melatonin.

Since melatonin levels decline sharply with age, it has been hypothesized that the reduction of melatonin levels

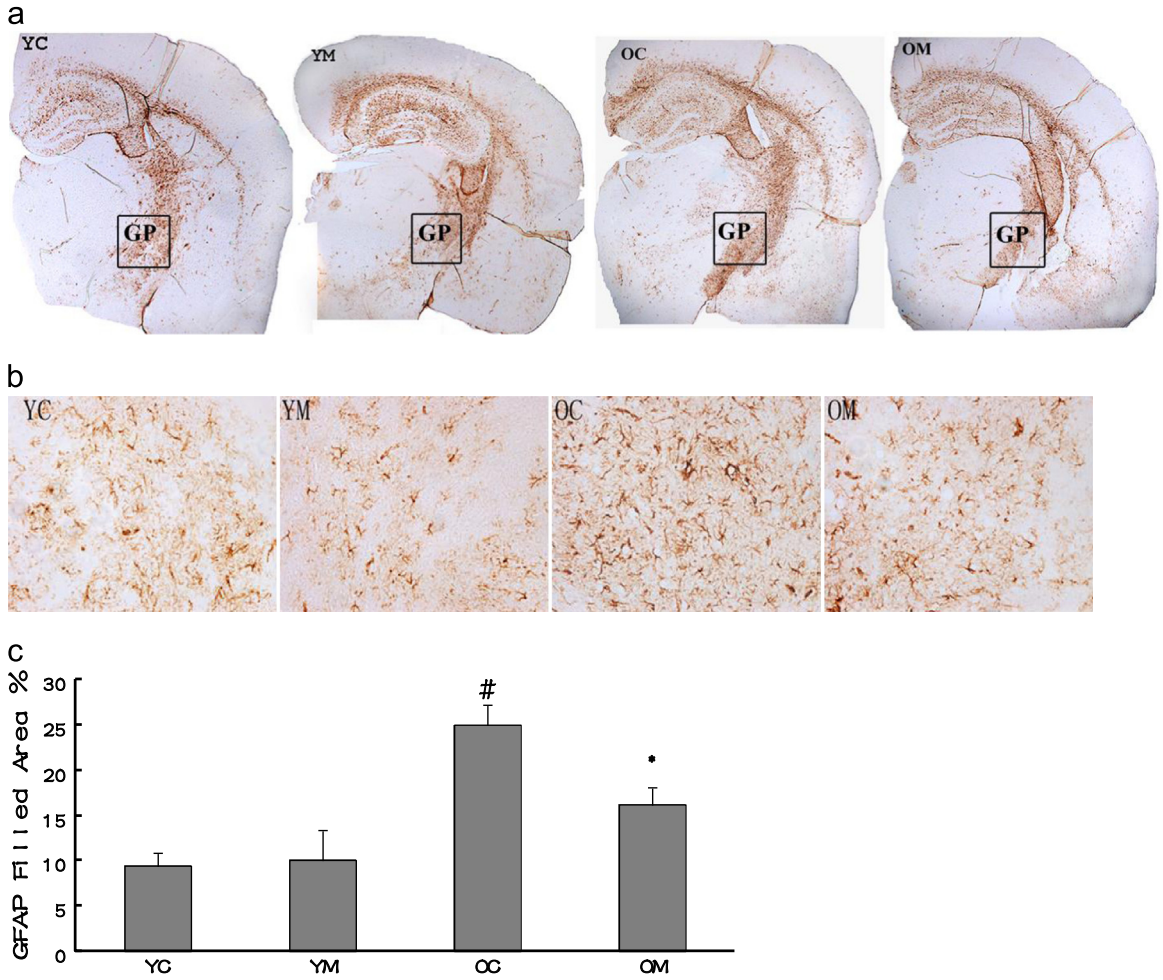

Fig. 1 – (a) Brain sections immunostained for GFAP. YC=young controls, YM=young melatonin-treated, OC=old control, OM=old melatonin-treated. (a) Magnification= ×40, GP=medial globus pallidus. Magnification= ×40. (b) Enlarged aspect of globus pallidus. Magnification= ×200. Arrows indicate activated astrocytes. (c) Quantitation of effect of melatonin treatment on GFAP and staining in globus pallidus (from (b)) of 5.5 and 23.4 month-old mice. Bars indicate mean of 11–12 animals, ±S.E.M. *: Value for mice treated with melatonin differs from value for corresponding untreated control of same age. #: Old control value differs from that of the young control ($p<0.05$).