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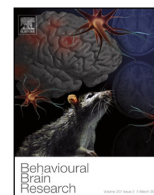

Research report

Melatonin reverses H-89 induced spatial memory deficit: Involvement of oxidative stress and mitochondrial function

Rojin Sharif[a], Mehdi Aghsami[a], Mehdi Gharghabi[a], Mehdi Sanati[a], Tina Khorshidahmad[a,b,c], Gelareh Vakilzadeh[a], Hajar Mehdizadeh[d], Shervin Gholizadeh[e], Ghorban Taghizadeh[d], Mohammad Sharifzadeh[a,*]

[a] Department of Pharmacology and Toxicology, Faculty of Pharmacy, Tehran University of Medical Sciences, P.O. Box 14155-6451, Tehran, Iran
[b] College of Pharmacy, University of Manitoba, 750 McDermot Avenue, Winnipeg, R3E 0T5, MB, Canada
[c] Manitoba Multiple Sclerosis Research Network Organization (MMSRNO), Winnipeg, Canada
[d] Department of Neuroscience, School of Advanced Science and Technologies in Medicine, Tehran University of Medical Sciences, Tehran, Iran
[e] Leslie Dan Faculty of Pharmacy, Department of Pharmaceutical Sciences, University of Toronto, M5S 3M2, Toronto, ON, Canada

HIGHLIGHTS

- Melatonin ameliorates H89 (Protein Kinase AII Inhibitor) related memory impairment.
- Melatonin prevents H89-induced oxidative and promotes antioxidative defense system.
- Melatonin impedes H89-mediated mitochondrial dysfunction and cytochrome *c* release.
- Melatonin can be used for oxidative-related neurodegenerative disorders.

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ABSTRACT

Oxidative stress and mitochondrial dysfunction play indispensable role in memory and learning impairment. Growing evidences have shed light on anti-oxidative role for melatonin in memory deficit. We have previously reported that inhibition of protein kinase A by H-89 can induce memory impairment. Here, we investigated the effect of melatonin on H-89 induced spatial memory deficit and pursued their interactive consequences on oxidative stress and mitochondrial function in Morris Water Maze model. Rats received melatonin (50 and 100 μg/kg/side) and H-89(10 μM) intra-hippocampally 30 min before each day of training. Animals were trained for 4 consecutive days, each containing one block from four trials. Oxidative stress indices, including thiobarbituric acid (TBARS), reactive oxygen species (ROS), thiol groups, and ferric reducing antioxidant power (FRAP) were assessed using spectrophotometer. Mitochondrial function was evaluated through measuring ROS production, mitochondrial membrane potential (MMP), swelling, outer membrane damage, and cytochrome *c* release. As expected from our previous report, H-89 remarkably impaired memory by increasing the escape latency and traveled distance. Intriguingly, H-89 significantly augmented TBARS and ROS levels, caused mitochondrial ROS production, swelling, outer membrane damage, and cytochrome *c* release. Moreover, H-89 lowered thiol, FRAP, and MMP values. Intriguingly, melatonin pre-treatment not only effectively hampered H-89-mediated spatial memory deficit at both doses, but also reversed the H-89 effects on mitochondrial and biochemical indices upon higher dose. Collectively, these findings highlight a protective role for melatonin against H-89-induced memory impairment and indicate that melatonin may play a therapeutic role in the treatment of oxidative- related neurodegenerative disorders.

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1. Introduction

The melatonin hormone (*N*-acetyl-5-methoxytryptamine), the chief product of the pineal gland, regulates circadian rhythms in mammals [1,2]. The pineal gland secretes less melatonin with aging, which in turn leads to the development of age-associated neurodegenerative disorders [1,3,4]. Consequently, a large number

* Corresponding author.
E-mail address: msharifzadeh@tums.ac.ir (M. Sharifzadeh).

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of experiments have focused on the role of melatonin therapy in a group of diseases linked to oxidative stress, such as neurodegenerative disorders, in particular Alzheimer's (AD) and Parkinson's disease [3–5].

The involvement of melatonin in manipulating hippocampus-dependent memories has been investigated in several previous studies [6]. In AD, the expression of the melatonin MT2 receptors in pyramidal and granular neurons of the hippocampus is significantly decreased [7,8]. More recent studies revealed a robust activity of this hormone against oxidative and nitrosative stress-induced damage in the brain [4,9]. Meanwhile, oxidative stress and mitochondrial dysfunction are major contributors to aging and neurodegenerative disorders, particularly by inducing neurodegeneration in the hippocampus [9–11]. Oxidative stress causes over-production of the reactive oxygen species (ROS) in the mitochondria, which thereby induces opening of mitochondrial permeability transition pores (MPTPs), leading to mitochondrial membrane swelling and collapse, as well as the release of cytochrome *c*, as a pro-apoptotic factor, which will eventually engender cell death [12–14]. Growing evidences have demonstrated that melatonin may improve learning and memory deficit due to its antioxidant properties [4,15]. As a potent antioxidant, melatonin exerts numerous functions, such as scavenging free radicals, stimulation of antioxidative enzymes formation, protecting mitochondrial ATP synthesis, preventing mitochondrial swelling, hampering MPTP opening, depolarization, cytochrome *c* efflux, and eventually, hindering apoptotic cell death [4,16,17]. Of further relevance, prior investigations have substantiated that amyloid-β 25–35-mediated memory and learning impairment or trauma-induced neural death can be circumvented by intraperitoneal (i.p.) melatonin injection, exerting its effects through blockade of proinflammatory factors expressions, lipid peroxidation reduction, and enhancement of antioxidative enzyme activities [18–20]. Consistent with this notion, another experiment has reported that melatonin can prevent mitochondrial ROS generation, MMP collapse, MPTP opening, which subsequently can impede cytochrome *c* release in rat brain astrocytes [21]. These studies jointly accentuate a pivotal role for melatonin in modulating hippocampal memory processes. In addition, there is evidence that administration of melatonin produced *N*1-acetyl-*N*2-formyl-5-methoxykynuramine (AFMK) and *N*1-acetyl-5-methoxykynuramine (AMK) as its major metabolites [22] which by modulating of mitochondrial function can protect neurons against reactive oxygen and nitrogen species [23–25].

On the other hand, recent findings by our group and others, have indicated that protein kinase A (PKA) regulates synaptic plasticity in hippocampus which eventually affects learning and memory [26]. Our previous studies in rats have also proposed that intra-hippocampal infusion of H-89, a selective PKAII inhibitor, impairs spatial memory formation in Morris water maze (MWM) task [27,28]. Since the role of melatonin on memory formation process through its interactive effect on H-89-induced mitochondrial dysfunction and oxidative stress has not been studied thus far, we aimed to interrogate the effects of melatonin, as a potent antioxidant, and H-89 induced spatial memory deficit using MWM method. Our findings underline melatonin treatment as a promising therapeutic intervention against mitochondrial and oxidative stress in neurological disorders.

2. Material and methods

2.1. Animals

Albino male Wistar rats (180–230 g) were obtained from the Faculty of Pharmacy, Tehran University of Medical Sciences. The animals were housed in groups of three in Plexiglas before surgery. They had free access to food and water and they were kept at room temperature (25 ± 2 °C) on a 12 h-light-dark cycle (lights on at 7 a.m.). The trainings were conducted during the light cycle at 1 p.m. All animal experiments were carried out in accordance with guidelines from the declaration of Helsinki for Care and Use of Laboratory animals (Publication No. 85–23, revised 1985).

2.2. Materials

Melatonin, H-89, ketamine, and xylazine were purchased from Sigma (St. Louis, MO, USA). H-89 was dissolved in DMSO (0.3%) and diluted afterwards with normal saline to final concentration of 10 μM. Melatonin was dissolved in absolute ethanol (100%) and diluted with normal saline to give a final concentration of ethanol less than 10% in stock solution and were kept below 4 °C before use. In order to prepare fresh melatonin solution, the stock was diluted with normal saline to the desired concentrations and administered at two selected doses (50 or 100 μg/kg/side). Doses of melatonin and H-89 were selected based upon prior studies [27–31]

2.3. Surgery

All the rats were anesthetized with an i.p. injection of ketamine (100 mg/kg) and xylazine (25 mg/kg). Animals were placed in stereotaxic instrument (Stoelting,Wood Dale, IL, USA), cannulated bilaterally in CA1 region of the hippocampus and fixed afterwards by orthopedic cement according to the atlas of Paxinos and Watson (3.8 mm posterior and 2.2 mm lateral to Bregma and 2.7 mm ventral to the surface of the skull) [32]. All behavioral experiments commenced one week after completion of surgeries, allowed as a recovery time, to minimize the potential effects of surgeries or the anesthetic procedure on behavioral training.

2.4. Melatonin and H-89 infusion

All microinjections were performed bilaterally through 21 gauge cannula using a polyethylene tube attached to a 27 gauge needle from one side and to a 10 μl Hamilton micro-syringe on the other side. In this study for reducing the effects of melatonin metabolites on memory function, we decided to administer melatonin locally rather than systematically in order to investigate the local and direct effects of melatonin on H89-induced mitochondrial and memory alterations. The elapsing period for administration and testing time was chosen according to the kinetic properties of melatonin [33,34] and previous investigations [27,28]. The infusion time for all injections was 2 min and needles were left in place for an additional 60 s in order to allow the drug to be absorbed completely. The infusion protocol carried out according to previous investigations.

2.5. Behavioral training and evaluation

All the rats were trained for 4 days in the MWM. Each day included one block and each block comprised of four trials. The maze consisted of a circular black pool (136 cm diameter, 60 cm height), filled to a depth of 35 cm with water (22 ± 2 °C). In the center of the North West quadrant of this pool, an invisible Plexiglas platform was located 1 cm under the water surface. In each trial, the rat was allowed to swim freely in the pool to find the hidden platform for 90 s. If the animal could not find the platform during this period, the investigator manually guided the rat to the platform. The task was repeated by releasing the rat from four different quadrants for each trial. The rats were allowed to rest for 30 s between the trials. Swimming paths were recorded using a video camera located above the pool, which was linked to a computer. Escape

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