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Melatonin-primed ADMSCs elicit an efficacious therapeutic response in improving high-fat diet induced non-alcoholic fatty liver disease in C57BL/6J mice

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Abstract

Background: Stem cells are widely used for therapy including treatment of liver damage. Adipose-derived mesenchymal stem cells (ADMSCs) administered to treat fatty liver are known to improve liver function but their use is restricted due to a poor success rate. This study investigates efficacy of melatonin-primed ADMSCs (Mel. MSCs) in experimentally induced non-alcoholic fatty liver disease (NAFLD).

Results: MSCs treated with LPS showed prominent DCFDA fluorescence as compared to the untreated cells. Also, the JC-1 staining had accounted for higher intensity of green monomer and a weak fluorescence of red dimer indicating weaker mitochondrial membrane potential. But melatonin co-treatment could make necessary corrective changes as evidenced by reverse set of results. The overall cell survival was also found to be improved following melatonin treatment as evidenced by the MTT assay. Also, the antioxidant (*Nrf2* and *Ho-1*) and anti-inflammatory genes (*Il-4* and *Il-10*) showed a decrement in their mRNA levels following LPS treatment whereas the pro-inflammatory genes (*Tnf-α*, *Il-6*, *Tlr-4*, and *Lbp*) showed a reciprocal increment in the said group. Melatonin co-treatment accounted for an improved status of antioxidant and anti-inflammatory genes as evidenced by their mRNA levels. High-fat high-fructose diet (HFFD) fed C57BL/6J mice recorded higher serum AST and ALT levels and fatty manifestation in histology of liver along with lowered mRNA levels of antioxidant (*Nrf2*, *Catalase*, and *Gss*) genes and Hgf. These set of parameters showed a significant improvement in HFFD + Mel.MSC group.

Conclusion: A significant improvement in viability of MSCs was recorded due to lowered intracellular oxidative stress and improves mitochondrial membrane potential. Further, melatonin-primed MSCs accounted for a significant decrement in fatty manifestations in liver and an improved physiological status of NAFLD in HFFD fed C57BL/6J mice. Taken together, it is hypothesized that melatonin priming to MSCs prior to its use can significantly augment the success of stem cell therapy.

Keywords: Melatonin, Non-alcoholic fatty liver disease, Stem cell therapy, Adipose-derived mesenchymal stem cells, NAFLD

Background

The ability of mammalian liver to undergo reparative regeneration in condition of hepatotoxic manifestations by a single or multiple factors is well established. Non-alcoholic fatty liver disease (NAFLD) is characterized by

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EXOGENOUS MELATONIN IMPROVES LIVER FUNCTION AND NEUROBEHAVIORAL DESYNCHRONY IN EXPERIMENTALLY INDUCED LIFE STYLE DISORDER IN C57BL/6J MICE

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Circadian clock modulation impairs cognitive performance, deficits in learning, memory and spontaneous locomotor activity. In mice, high fat high fructose diet (HFFD) alone or in combination with photoperiodic manipulations modulates the circadian clock that culminates in fatty manifestations in liver and behavioral perturbations. We hypothesize that timed administration of melatonin improves liver functions and behavior in experimentally induced model of lifestyle disorder. C57BL/6J mice were subjected to photoperiodic shifts alone or in combination with HFFD for a period of 18 weeks. Both the experimental regimens resulted in development of fatty manifestations in liver. Development of NASH was confirmedby lipid profile and histomorphology. Later, mice were subjected to behavioral tests (open field, OFT; elevated plus maze, EPM; force swim, FST; sucrose preference, SPT; tail suspen- sion, TST; Barnes maze, BMT and Morris water maze, MWM tests) to evaluate spontaneous locomotor activity, anxiety, depression and memory. Further, synaptic plasticity, inflamma- tion, neurotrophins and dendritic spine density in the hippocampus were assessed.

Results: ALT, AST levels, total lipids, TGs, LDL-C, VLDL-C and cortisol were significantly higher in CD, HFFD and HFFD+CD group whereas, exogenous melatonin treatment accounted for corrective changes. Ballooning hepatocytes with distorted hepatic chords and fatty changes observed in CD, HFFD and HFFD+CD groups too were significantly lowered in melatonin treated group. HFFD or HFFD+CD groups showed significantly increased body weight, hair coat index and significant negative impact on spontaneous locomotor (OFT) activity. Also, results obtained in EPM confirmed anxiety whereas; FST, TST and SPT had confirmed depression in mice. The memory appeared to be negatively affected as evidenced by results obtained in BMT and MWM tests. Exogenous melatonin showed moderate to significant improvement in the said parameters as evidenced by the results of behavioral studies. It was further confirmed by mRNAs of key genes governing anxiogenic changes, impaired spatial learning and variability in locomotor activity in hippocampal region of control and treated mice. Reduced Nissl positive neurons, down regulation of synaptic plasticity (BDNF, SYN-1 and PSD-95) and increment in pro-inflammatory cytokines were recorded in HFFD, CD and HFFD+CD mice. The said behavioral distortions, neurotrophic growth factors and synaptic markers expression were found to be reversed, ranging from moderate to significant level in melatonin treated group.

Conclusion: Findings suggest that exogenous melatonin improves liver function and hippocampal synaptic plasticity in experimental model of lifestyle disorder. The same culminating in gross improvement in motor indices as evidenced by the improvement in indices of behavior is the highlight of the study.

AASLD Abstracts

Circadian basis of nonalcoholic steatohepatitis: Inflammation management as a keystone in conventional and modern therapeutic strategies

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Summary

Circadian clock oscillators regulate the suprachiasmatic nucleus (SCN) or the circadian core clock and coordinate functioning of various peripheral clocks in blood cells, heart, lungs, gut, liver etc. The SCN synchronizes peripheral liver clock via. the photoperiod, temperature, and feeding regimen that further impacts the homeostasis of glucose, lipid and cholesterol metabolism. In mammals, circadian networks are mainly regulated by transcription-translation feedback loop of *Brain and Muscle ARNT-Like 1 (Bmal 1). Clock* heterodimer which drives transcription and translation of Period-1 (*Per-1)*, *Per-2*, *Per-3*, Cryptochrome Circadian Regulator 1 (*Cry-1)*, *Cry-2*, and *Rev-erbs*. Disturbance of circadian rhythms by environmental and genetic factors or lifestyle perturbations have been strongly implicated as causative agents for nonalcoholic fatty liver disease (NAFLD) and/or nonalcoholic steatohepatitis (NASH). Enlargement of adipocytes, macrophage recruitment and a persistent inflammation are the hallmarks of NAFLD that progress to NASH. In adipose tissue, incoherence in M1/M2 macrophages' ratio triggers the production and secretion of proinflammatory adipocytokines. *In vitro* studies have demonstrated that activation of M2 macrophages is initiated by anti-inflammatory cytokines IL-4 and IL-10 in experimentally induced ER-stress in HepG2 cells. Inflammasome dependent activation of IL-1β and IL-18 are also important mediators and crucial in the progression of NAFLD to NASH. Owing to the multifactorial nature of NASH, there is no single FDA approved drug available till date. Traditional medicines or the modern therapeutic strategies include herbal medicines, modifications in lifestyle, phytopharmacotherapy, stem cell-based therapy, and synthetic drugs. However, PPAR agonists, bile acid sequestrants, incretin-based therapy, lipid lowering drugs, gut and microbiome therapies etc. have emerged as modern therapeutants that target various facets of NASH progression. But, after the onset of fibrotic changes in liver, these drugs have limited efficacy due to the irreversible nature of pathophysiological damage inflicted by the disease. Hence, targeting inflammation during the early phase of NASH till date appears to be the most tangible option as a therapy. Herein, we discuss the inflammatory sojourn underlying mechanism of onset and progression of NAFLD to NASH and the regulatory gene targets. Further, this chapter compiles the merits of traditional and modern therapeutants and their systemic and molecular targets in lowering inflammation either directly or via making corrective changes in clock gene function.

Systemic and hepatic circadian clocks

The impact of lifestyle modifications, globalization and industrialization has increased the occurrence of cardiovascular diseases, diabetes and metabolic syndrome. The extensive use of artificial light at night, long-distance transcontinental travel and shift work time coupled with a high calorie diet have intensively altered the biological clock with a negative impact on health

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RESEARCH ARTICLE

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Melatonin induces Nrf2-HO-1 reprogramming and corrections in hepatic core clock oscillations in Non-alcoholic fatty liver disease

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Abstract

Melatonin pleiotropically regulates physiological events and has a putative regulatory role in the circadian clock desynchrony-mediated Non-alcoholic fatty liver disease (NAFLD). In this study, we investigated perturbations in the hepatic circadian clock gene, and Nrf2-HO-1 oscillations in conditions of high-fat high fructose (HFHF) diet and/or jet lag (JL)-mediated NAFLD. Melatonin treatment (100 μM) to HepG2 cells led to an improvement in oscillatory pattern of clock genes (*Clock, Bmal1*, and *Per*) in oleic acid (OA)-induced circadian desynchrony, while *Cry, Nrf2*, and *HO-1* remain oblivious of melatonin treatment that was also validated by circwave analysis. C57BL/6J mice subjected to HFHF and/or JL, and treated with melatonin showed an improvement in the profile of lipid regulatory genes (*CPT-1, PPARa, and SREBP-1c*), liver function (AST and ALT) and histomorphology of fatty liver. A detailed scrutiny revealed that hepatic mRNA and protein profiles of Bmal1 (at ZT6) and Clock (at ZT12) underwent corrective changes in oscillations, but moderate corrections were recorded in other components of clock genes (Per1, Per2, and Cry2). Melatonin induced changes in oscillations of anti-oxidant genes (Nrf2, HO-1, and Keap1) subtly contributed in the overall improvement in NAFLD recorded herein. Taken together, melatonin induced reprograming of hepatic core clock and Nrf2-HO-1 genes leads to an improvement in HFHF/JL-induced NAFLD.

KEYWORDS
clock genes, melatonin, NAFLD, Nrf2-HO-1

1 | INTRODUCTION

Circadian rhythms are the internal biological clock that orchestrates various physiological events of metabolic processes in mammals.[1] The suprachiasmatic nucleus (SCN) is the central pacemaker of the biological clock, while peripheral clocks in various organs are operated by autoregulatory expression of clock genes.[2] The molecular network comprises of circadian locomotor output cycles kaput (Clock) and brain and muscle ARNT-like 1 (Bmal1) as activators,

Abbreviations: ARE, antioxidant response elements; Bmal1, brain and muscle ARNT-like 1; Clock, circadian locomotor output cycles kaput; Cry1-2, cryptochrome circadian regulator 1; HFHF, high fat high fructose; HO-1, heme oxygenase 1; JL, jet lag; Keap1, Kelch-like ECH-associated protein 1; NAFLD, non-alcoholic fatty Liver disease; Nrf2, nuclear factor erythroid 2-related factor 2; OA, oleic acid; Per1-2, period circadian protein homolog 1 and 2; SCN, suprachiasmatic nucleus; ZT, zeitgebers time.

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Research Paper

Carbon monoxide releasing molecule-A1 improves nonalcoholic steatohepatitis via Nrf2 activation mediated improvement in oxidative stress and mitochondrial function

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ABSTRACT

Nuclear factor-erythroid 2 related factor 2 (Nrf2)-mediated signaling plays a central role in maintaining cellular redox homeostasis of hepatic cells. Carbon monoxide releasing molecule-A1 (CORM-A1) has been reported to stimulate up-regulation and nuclear translocation of Nrf2 in hepatocytes. However, the role of CORM-A1 in improving lipid metabolism, antioxidant signaling and mitochondrial functions in nonalcoholic steatohepatitis (NASH) is unknown. In this study, we report that CORM-A1 prevents hepatic steatosis in high fat high fructose (HFHF) diet fed C57BL/6J mice, used as model of NASH. The beneficial effects of CORM-A1 in HFHF fed mice was associated with improved lipid homeostasis, Nrf2 activation, upregulation of antioxidant responsive (ARE) genes and increased ATP production. As, mitochondria are intracellular source of reactive oxygen species (ROS) and important sites of lipid metabolism, we further investigated the mechanisms of action of CORM-A1-mediated improvement in mitochondrial function in palmitic acid (PA) treated HepG2 cells. Cellular oxidative stress and cell viability were found to be improved in PA + CORM-A1 treated cells via Nrf2 translocation and activation of cytoprotective genes. Furthermore, in PA treated cells, CORM-A1 improved mitochondrial oxidative stress, membrane potential and rescued mitochondrial biogenesis thru upregulation of Drp1, TFAM, PGC-1α and NRF-1 genes. CORM-A1 treatment improved cellular status by lowering glycolytic respiration and maximizing OCR. Improvement in mitochondrial respiration and increment in ATP production in PA + CORM-A1 treated cells further corroborate our findings. In summary, our data demonstrate for the first time that CORM-A1 ameliorates tissue damage in steatotic liver via Nrf2 activation and improved mitochondrial function, thus, suggesting the anti-NASH potential of CORM-A1.

1. Introduction

Multitude of metabolic diseases, including non-alcoholic steatohepatitis (NASH), have been implicated to higher consumption of fat-rich and high calorie foods [1]. About 15% of the total obese individuals with symptoms of metabolic syndrome constitute the high-risk group for NASH. Ethnicity, dietary habits, genetic and environmental factors further contribute towards the observed variations in occurrence of NASH [2,3]. Excess lipid accumulation in hepatocytes, high oxidative stress and inflammation are the key players in pathogenesis of NASH [4]. Currently used symptomatic treatment protocols for NASH include the lipid lowering, anti-diabetic, antioxidants or anti-inflammatory drugs coupled with changes in lifestyle. However, no FDA approved drug is presently available for this potentially lethal disease [5]. Patients with NASH develop anomalies in the ultrastructure of mitochondria, impairment of hepatic ATP synthesis and increased mitochondrial ROS production [6,7]. Lipid peroxidation, cytokine production and fatty manifestations in liver causes cell death and overall impairment of liver function [8].

The transcription factor nuclear factor erythroid 2-related factor 2

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HSP60 knockdown exerts differential response in endothelial cells and monocyte derived macrophages during atherogenic transformation

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Ectopic expression of HSP60 in vascular cells is known to activate auto-immune response that is critical to atherogenic initiation. However, the pathogenic relevance of the aberrant HSP60 upregulation in intracellular signaling pathways associated with atherogenic consequences in vascular cells remains unclear. The aim of the present study was to determine the role of endogenous HSP60 in atherogenic transformation of endothelial cells and macrophages. After generating primary evidence of oxidized low density lipoprotein (OxLDL) induced HSP60 upregulation in human umbilical vein endothelial cells (HUVEC), its physiological relevance in high fat high fructose (HFHF) induced early atherogenic remodelling was investigated in C57BL/6J mice. Prominent HSP60 expression was recorded in tunica intima and media of thoracic aorta that showed hypertrophy, lumen dilation, elastin fragmentation and collagen deposition. Further, HSP60 overexpression was found to be prerequisite for its surface localization and secretion in HUVEC. eNOS downregulation and MCP-1, VCAM-1 and ICAM-1 upregulation with subsequent macrophage accumulation provided compelling evidences on HFHF induced endothelial dysfunction and activation that were also observed in OxLDL treated- and HSP60 overexpressing-HUVEC. OxLDL induced concomitant reduction in NO production and monocyte adhesion were prevented by HSP60 knockdown, implying towards HSP60 mediated possible regulation of the said genes. OxLDL induced HSP60 upregulation and secretion was also recorded in THP-1 derived macrophages (TDMs). HSP60 knockdown in TDMs accounted for higher OxLDL accumulation that correlated with altered scavenger receptors (SR-A1, CD36 and SR-B1) expression further culminating in M1 polarization. Collectively, the results highlight HSP60 upregulation as a critical vascular alteration that exerts differential regulatory role in atherogenic transformation of endothelial cells and macrophages.

Development of early atherosclerotic lesion is preceded by endothelial cell (EC) dysfunction involving impairment of nitric oxide (NO)-mediated vaso-relaxation. These changes in EC are accompanied by loss of barrier function allowing the sub-endothelial accumulation of low density lipoprotein (LDL). Simultaneous expression of adhesion molecules including intercellular cell adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and E-selectin on EC cell surface along with secretion of chemokines like macrophage chemoattractant protein-1 (MCP-1), facilitates sub-intimal recruitment of macrophages that marks the initiation of early atherosclerotic lesions. The resultant inflammation mediates vascular remodelling that gradually culminates in development of atheromatous plaques[1,2]. Thus, EC dysfunction is a critical event that triggers the development of atherosclerotic lesions and it is imperative to understand the underlying molecular mechanisms.

The development of mature atheromatous plaque primarily involves internalization of oxidized LDL (OxLDL) by macrophages and their transformation into foam cells[3]. The uptake of OxLDL via scavenger receptors (SRs), such as scavenger receptor class A type 1 (SR-A1) and cluster of differentiation 36 (CD36), and subsequent receptor-mediated endocytosis activates a cascade of pathogenic events involving mitochondrial depolarization, generation of reactive oxygen species (ROS) as well as upregulation of SRs[4]. Apart from uptake, the degree of

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Carbon monoxide releasing molecule A-1 attenuates acetaminophen-mediated hepatotoxicity and improves survival of mice by induction of Nrf2 and related genes

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ABSTRACT

Acute liver injury is frequently associated with oxidative stress. Here, we investigated the therapeutic potential of carbon monoxide releasing molecule A-1 (CORM A-1) in oxidative stress-mediated liver injury. Overnight-fasted mice were injected with acetaminophen (APAP; 300 mg/kg; intraperitoneally) and were sacrificed at 4 and 12 h. They showed elevated levels of serum transaminases, depleted hepatic glutathione (GSH) and hepatocyte necrosis. Mice injected with CORM A-1 (20 mg/kg) 1 h after APAP administration, had reduced serum transaminases, preserved hepatic GSH and reduced hepatocyte necrosis. Mice that received a lethal dose of APAP (600 mg/kg), died by 10 h; but those co-treated with CORM A-1 showed a 50% survival. Compared to APAP-treated mice, livers from those co-treated with CORM A-1, had upregulation of Nrf2 and ARE genes (HO-1, GCLM and NQO-1). APAP-treated mice had elevated hepatic mRNA levels of inflammatory genes (Nf-κB, TNF-α, IL1-β and IL-6), an effect blunted in those co-treated with CORM A-1. In *tert*-butyl hydroperoxide (t-BHP)-treated HepG2 cells, CORM A-1 augmented cell viability, reduced oxidative stress, activated the nuclear factor erythroid 2–related factor 2 (Nrf2) and anti-oxidant response element (ARE) genes. The molecular docking profile of CO in the kelch domain of Keap1 protein suggested that CO released from CORM A-1 mediated Nrf2 activation. Collectively, these data indicate that CORM A-1 reduces oxidative stress by upregulating Nrf2 and related genes, and restoring hepatic GSH, to reduce hepatocyte necrosis and thus minimize liver injury that contributes to an overall improved survival rate.

1. Introduction

Liver detoxifies endogenous metabolites and xenobiotics generated after medication ingestion and thus remains at risk for injury due to generation of free radicals or reactive oxygen species (ROS) (Yan et al., 2009). Liver has a robust antioxidant defense system that plays key role in modulating drug-induced liver injury (DILI) (Zhu et al., 2012). Therefore, hepatoprotective agents—that enhance cellular antioxidant defense system, scavenge free radicals and reduce the risk of ROS induced damage—have potential in treating DILI (Jadeja et al., 2016a). Acetaminophen (*N*-acetyl-p-aminophenol, APAP) is a widely used antipyritic whose overdose is the most common cause of DILI (Nourjah et al., 2006; Liu et al., 2012; Urrunaga et al., 2015). After APAP overdose, the sulfation and glucuronidation pathways are saturated leading to increased APAP metabolism by hepatic cytochrome P-450 (CYP450) (Urrunaga et al., 2015). This leads to generation of *N*-acetyl-p-benzoquinone imine (NAPQI), a highly toxic metabolite that depletes GSH stores, binds to cellular proteins and induces necrosis, which initiates sterile inflammation (Knight et al., 2002; Saito et al., 2010; Jaeschke et al., 2012a). *N*-acetyl cysteine (NAC), a precursor of cellular GSH biosynthesis, is the only FDA-approved antidote for APAP-induced hepatotoxicity (Heard and Green, 2012). However, NAC has a narrow rescue window; treatment response is best when NAC is administered within 8 h of APAP overdose (Kerr et al., 2005; Whyte et al., 2007).

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RESEARCH Open Access

Chronic photoperiodic manipulation induced chronodisruption upregulates HSP60 during early pro-atherogenic remodeling in thoracic aorta of C57BL/6J mice

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Abstract

Background: Circadian disruption is often associated with aggravation of atherosclerosis; however, the pathophysiological mechanisms underlying atherogenic initiation in normolipidemic diet remains unclear. Most of the studies done for understanding circadian disruption induced atherosclerosis have been carried out in murine model of hyperlipidemia induced atherosclerosis. The present study investigates pro-atherogenic events in response to chronic photoperiodic manipulation induced chronodisruption (PMCD) in C57BL/6J mice fed with laboratory chow diet.

Results: The results were compared with atherogenic initiation induced by high fat high fructose (HFHF) diet. The combined effects of HFHF and PMCD on atherogenic initiation were also investigated for possible synergy of both variants. The HFHF and HFHF+PMCD groups recorded increments in body weight gains and serum lipid parameters (TC, TG, LDL-cholesterol, VLDL) and a decrement in HDL-cholesterol as compared to the control group. However, PMCD group recorded body weight gain similar to that of the control group, but the serum lipid parameters (TG and VLDL) were significantly elevated and the HDL levels were lowered. However, prominent hypertrophic remodeling, higher collagen deposition, and elastin derangement, along with endothelial dysfunction, its activation, and macrophage infiltration, were observed in thoracic aorta of all the three experimental groups. But the mRNA and immunoblots of heat shock protein 60 (HSP60) in thoracic aorta was found to be maximum in PMCD followed by HFHF and HFHF+PMCD groups.

Conclusion: Laboratory chow feeding coupled with photoperiodic manipulation mediated chronodisruption overexpress HSP60 that in turn plays a central role in PMCD mediated pro-atherogenic remodeling in thoracic aorta of C57BL/6J mice.

Keywords: Atherosclerosis, HSP60, Chronodisruption, Vascular remodeling, High fat high fructose diet

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