Melatonin and Metabolic Disorders: Unraveling the Interplay With Glucose and Lipid Metabolism, Adipose Tissue, and Inflammation

Seok Hyun Hong, MS¹, Jinkwan Kim, MPH, PhD¹ ²
¹Department of Biomedical Laboratory Science, College of Health Science, Jungwon University, Goesan, Korea
²Sleep Medicine Institute, Jungwon University, Goesan, Korea

The increasing prevalence of metabolic disorders such as cardiovascular disease, type 2 diabetes, and obesity, highlighted the crucial need to understand the intricate mechanisms that contribute to these health conditions. Melatonin, produced by the pineal gland in the brain, plays a crucial role in regulating the sleep-wake cycle and has been widely studied for its potential health benefits. Recognized for its pivotal involvement in the sleep-wake cycle, melatonin exhibits various physiological functions such as its antioxidant and anti-inflammatory properties. Moreover, a growing body of evidence has suggested a potential association between melatonin and metabolic disorders, particularly those related to insulin resistance, obesity, and diabetes. In this review, we clarify the influence of melatonin on insulin sensitivity and its role in glucose and lipid metabolism, highlighting its potential to address pivotal factors contributing to metabolic disorders. In addition, the complex relationship between melatonin and adipose tissue dynamics is explored to elucidate the hormone's involvement in the conversion of white fat to beige fat and its subsequent implications for energy expenditure. We briefly summarize a comprehensive discussion of the therapeutic implications of melatonin, provide insights into potential avenues for future research, and emphasize the importance of adopting a comprehensive approach to metabolic disorders.

INTRODUCTION

Metabolic disorders present a significant challenge to global health due to a growing public health crisis, affecting over one billion people worldwide [1,2]. Among the conditions associated with metabolic dysfunction including obesity, non-alcoholic fatty liver disease, and especially type 2 diabetes mellitus, dysregulation of glucose and lipid metabolism, chronic low-grade inflammation, and dysfunctional adipose tissue physiology have been proposed as important predictors of increased risk of cardiovascular disease [3]. Metabolic disorders encompass a wide range of conditions that affect the body’s ability to process and use energy effectively. While this category includes various disorders such as metabolic syndrome, mitochondrial disorders, and inborn errors of metabolism, this discussion will specifically focus on two common and impactful metabolisms: glucose and lipid.

Current therapeutic approaches for addressing the increasing burden of metabolic dysfunction have shown limited and short-lived effectiveness [4-6]. Although intensive research has been conducted to elucidate drug and lifestyle interventions targeting various aspects of metabolic dysregulation, therapeutic success in translational settings remains limited due to...
Oversimplification of the complex and multifactorial pathogenesis [3,5,6]. Pharmacological therapies typically attempt to modify individual aspects, such as improving insulin sensitivity or reducing inflammatory mediators. However, they often fail to restore integrated homeostasis that encompasses interconnected glucose, lipid, and immune pathways [3,7,8]. This highlights the urgent need to readjust therapeutic modalities to the complex puzzle of metabolic impairments. Such biomimetic approaches, which address the heterogeneity of metabolic disorders with correspondingly multifaceted therapeutic actions, have the potential to sustainably address the substantial global burden of cardiovascular and glycemic complications.

Melatonin is a hormone secreted by the pineal gland that has a wide range of bioactivities, including metabolic regulation [9,10]. Preclinical data suggest that melatonin may have beneficial effects on insulin signaling, adipocyte differentiation, and lipid metabolism in obesity, as well as inflammation in diabetes and associated comorbidities [10,11]. Therefore, melatonin may be a useful supplement for addressing the complex pathogenesis of metabolic disorders. This review systematically synthesizes clinical and preclinical findings to uncover previously underappreciated connections between melatonin and metabolic dysfunction. The analysis focuses on the mechanistic regulation of glucose and lipid metabolism, adipose tissue inflammation and dynamics, and the therapeutic implications for clinical translation. The primary objective of this review is to present important findings that can help harness the therapeutic potential of melatonin to effectively address the global issue of metabolic disorders.

OVERVIEW OF MELATONIN METABOLISM: A COMPREHENSIVE INSIGHT

Melatonin is a neurohormone synthesized primarily in the pineal gland. Its availability and functionality within the body are dictated by a complex series of molecular transformations [9,10]. The initial step in melatonin synthesis involves the hydroxylation of tryptophan to 5-hydroxytryptophan (5-HTP), catalyzed by the enzyme tryptophan hydroxylase 1 (TPH1). This rate-limiting step sets the stage for subsequent melatonin production. TPH1-mediated hydroxylation is followed by the decarboxylation of 5-HTP to serotonin (5-hydroxytryptamine, 5-HT) via aromatic amino acid decarboxylase (AADC). Serotonin is then acetylated by serotonin-N-acetyltransferase (SNAT), leading to the formation of N-acetylserotonin (NAS). NAS is finally methylated by acetylserotonin O-methyltransferase (ASMT). Conversely, darkness removes this inhibition, allowing for increased melatonin production during the night. Melatonin is released from the pineal gland into the bloodstream, where it circulates and affects various tissues and organs [12,14]. Extra-pineal tissues, such as the gastrointestinal tract, retina, and immune cells, also contribute to melatonin synthesis, increasing its overall systemic availability [12,14,15]. The liver primarily degrades melatonin enzymatically. Melatonin is converted to 6-hydroxymelatonin by cytochrome P450 monoxygenases, specifically CYP1A2, CYP2C19, and CYP2C9. The resulting 6-hydroxymelatonin is then metabolized to sulfated and glucuronidated conjugates, which are excreted in the urine.

The effect of melatonin is mediated through specific receptors, primarily MT1 and MT2, and its activation initiates intracellular signaling cascades, influencing various physiological processes. In addition to regulating circadian rhythms, melatonin exhibits a wide range of physiological functions [10,12-14]. The suprachiasmatic nucleus, which serves as the internal clock in the human body, controls the circadian release of melatonin. Melatonin peaks at night and declines with exposure to light. Melatonin exerts its effects by interacting with specific receptors, primarily the MT1 and MT2 receptors, which are found in various tissues. This allows melatonin to influence diverse physiological processes, including immune modulation [13], antioxidant activity [14], and anti-inflammatory activity [16]. In recent years, extensive research has revealed melatonin as an important metabolic regulator, influencing glucose and lipid metabolism and helping maintain glucose and lipid homeostasis [10,17]. Additionally, studies suggest that melatonin may improve insulin sensitivity, indicating its potential therapeutic efficacy in treating insulin resistance—a primary pathophysiological abnormality underlying metabolic disease states [9,10]. The effect of melatonin on adipose tissue is significant, it is involved in the conversion of white adipose tissue (WAT) to metabolically active beige adipose tissue, a process known as browning [11,18]. This conversion has a significant impact on energy homeostasis, including energy expenditure and metabolic balance. To fully understand the multifaceted contributions of melatonin to human health and disease, it is essential to elucidate its intricate physiological actions in cells and tissues.

THE EFFECT OF MELATONIN ON GLUCOSE METABOLISM

Insulin Sensitivity and Signaling

Melatonin has been implicated in improving insulin sensitivity through multiple molecular pathways. A key mechanism involves the activation of insulin receptor substrate (IRS) proteins, which enhance insulin signaling cascades and promote glucose uptake in target tissues [9,19]. In addition, melatonin affects the Akt/glycogen synthase kinase-3β (GSK-3β) signal-
Regulation of Glucose Transporters and Glycolytic Enzymes by Melatonin

Recent studies suggest that melatonin may regulate glucose homeostasis by modulating key regulatory proteins involved in cellular glucose uptake and subsequent metabolism (Table 1) [9,10]. Melatonin has been found to increase the expression of mRNA and protein expression of the prominent glucose transporters GLUT1, GLUT3, and GLUT4 in various tissues [10,17]. The increased glucose influx via GLUT4 has been linked to the insulin-sensitizing effects of melatonin under metabolic conditions [23]. Melatonin increases glucose uptake into cells by activating receptor-mediated IRS-PI3k-Akt signaling and inducing translocation of GLUT transporters to the plasma membrane [10]. In addition, melatonin upregulates rate-limiting glycolytic enzymes such as hexokinase, phosphofructokinase, and pyruvate kinase to further enhance downstream glucose metabolism. Melatonin has the potential to improve cellular glucose utilization and reduce excessive postprandial glucose spikes by affecting proteins that regulate glucose uptake and glycolysis [23]. This is particularly relevant in diabetes, where glycolytic defects and impaired GLUT functionality may accelerate glycemic dysregulation [13]. Overall, the synergistic effects of indoleamine on proteins that support glucose influx and glycolysis make it an attractive adjunctive strategy for optimizing glycemic control in metabolic disease [10]. Ongoing research should continue to determine the optimal melatonin doses for clinical translation of these mechanistic benefits.

Table 1. The key function of melatonin related to metabolic function

<table>
<thead>
<tr>
<th>Function</th>
<th>Description</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose metabolism</td>
<td>Improves insulin sensitivity</td>
<td>Enhances insulin receptor signaling, Akt/GSK-3β pathway; increases glucose uptake</td>
</tr>
<tr>
<td>Regulates glucose transporters and glycolytic enzymes</td>
<td>Regulates glucose transporters and glycolytic enzymes</td>
<td>Upregulates GLUT and glycolysis enzymes; augments cellular glucose influx and utilization</td>
</tr>
<tr>
<td>Protects mitochondrial function</td>
<td>Protects mitochondrial function</td>
<td>Reduces oxidative damage; regulates mitochondrial biogenesis, autophagy and membrane potential; maintains energy homeostasis</td>
</tr>
<tr>
<td>Lipid metabolism</td>
<td>Influences enzymes and proteins involved in lipid metabolism</td>
<td>Modulates cholesterol synthesis and lipoprotein lipase; affects triglyceride storage/breakdown and lipid mobilization</td>
</tr>
<tr>
<td>Regulates adipocyte differentiation and fat accumulation</td>
<td>Activates thermogenesis</td>
<td>Inhibits preadipocyte differentiation and adipogenesis via PPARγ and Wnt/β-catenin pathways; increases brown fat UCP1 expression and beige fat transformation; boosts energy expenditure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[11,17,22,23,46]</td>
</tr>
<tr>
<td></td>
<td>Exhibits antioxidant effects</td>
<td>Directly scavenges reactive oxygen species; upregulates antioxidant enzymes</td>
</tr>
<tr>
<td></td>
<td>Attenuates inflammation</td>
<td>Inhibits NF-κB pathway, inflammasome activation, and release of proinflammatory cytokines</td>
</tr>
</tbody>
</table>

GSK-3β, glycogen synthase kinase-3β; GLUT, glucose transporter; PPARγ, peroxisome proliferator-activated receptor gamma; UCP1, uncoupling protein 1; NF-κB, nuclear factor-kappa B.
Mitochondrial Function and Cellular Energy Balance

Mitochondria are essential for energy production through oxidative phosphorylation [14]. Melatonin may play a protective role in maintaining cellular energy homeostasis [14,24], as well as inhibiting oxidative stress, a pathological condition that may contribute to the onset of mitochondrial dysfunction (Table 1) [14,19]. In addition to its antioxidant properties, it appears to affect the dynamics of mitochondrial biogenesis and autophagy [14,25]. It has been associated with the upregulation of critical regulators of mitochondrial biogenesis, such as the peroxisome proliferator-activated receptor gamma (PPAR-γ), which promote the formation of new mitochondria [24,26]. Concurrently, melatonin may also enhance mitophagy, the selective autophagic turnover of damaged mitochondria, thereby maintaining a healthy population of mitochondria in cells [27,28]. The interaction between the hormone and mitochondrial function extends to the regulation of the mitochondrial membrane potential, which is an indicator of mitochondrial health and function. Melatonin helps maintain this potential by ensuring efficient adenosine triphosphate (ATP) production, which is essential for various cellular processes that require energy [23,24]. In addition, melatonin stabilizes the inner mitochondrial membrane, preventing the release of cytochrome c, a pro-apoptotic factor, and thereby inhibiting cell death pathways [24,29]. Through these effects, melatonin is implicated in the regulation of cellular energy metabolism [23]. It affects enzymes involved in the glycolytic pathway, which impacts metabolic flux and energy yield [13]. This modulation is crucial under conditions of metabolic stress, where the presence of melatonin can shift cellular metabolism to a more protective state, ensuring energy conservation and reducing the generation of potentially harmful by-products [17]. The association of melatonin with mitochondrial function has potential therapeutic implications for a wide range of diseases in which mitochondrial dysfunction is a contributing factor, such as metabolic disorders [9,10], neurodegenerative diseases [13], and aging [16]. The hormone’s ability to increase mitochondrial efficiency and protect against oxidative damage may provide a basis for novel interventions aimed at restoring energy balance in diseased or aging cells [24,26]. In summary, the association between melatonin and mitochondrial function is an important aspect of its biological activity. Protective effects of melatonin on mitochondrial integrity and function contribute to its role in maintaining cellular energy balance. This relationship holds promise for the development of therapeutic strategies targeting mitochondrial-related diseases and conditions characterized by altered energy homeostasis. However, further research is needed to fully understand these interactions and their implications for clinical practice.

Lipid metabolism, which includes the synthesis, storage, and utilization of fats, plays a critical role in maintaining metabolic homeostasis. Recent research has revealed a fascinating interplay between melatonin, the neurohormone best known for its role in the regulation of the sleep-wake cycle, and lipid metabolism (Table 1) [23]. The effect of melatonin on lipid metabolism is multifaceted, affecting both lipid synthesis and utilization. Studies have suggested that melatonin may exert regulatory effects on key enzymes involved in lipid biosynthesis, influencing processes such as lipogenesis in the liver. In addition, melatonin has been implicated in the modulation of lipolysis, the breakdown of fats into fatty acids, particularly in adipose tissue [11]. These findings suggest a potential role for melatonin in the regulation of lipid storage and mobilization. Moreover, melatonin exhibits a time-dependent regulation of lipid metabolism, with variations over the 24-hour circadian cycle [30]. The level of melatonin typically increases during the dark phase, coinciding with increased lipid metabolism in various tissues. This synchronization of the circadian rhythm implies a temporal coordination between melatonin and lipid-related processes, highlighting the importance of considering the timing of interventions in studies investigating the relationship between melatonin and lipid metabolism. While the precise mechanisms underlying the effect of melatonin on lipid metabolism are still being elucidated, emerging evidence underscores the potential of the hormone as a regulator of lipid homeostasis.

Effect of Melatonin on Adipocyte Differentiation and Fat Accumulation

Adipocyte differentiation, or adipogenesis, is the process by which pre-adipocytes, or undifferentiated fibroblast-like cells, become mature adipocytes [11,18]. These cells specialize in storing energy as fat and are essential for maintaining energy homeostasis in the body [31,32]. Adipogenesis plays an important role in obesity and related metabolic disorders [31]. Recent studies have implicated melatonin in adipocyte differentiation and fat accumulation (Table 1) [29,33]. This association is particularly relevant in the context of the global rise in obesity rates and metabolic syndrome, which are conditions characterized by increased adiposity [1-3]. Moreover, studies suggest that melatonin may modulate adipogenesis by interacting with melatonin receptors present on preadipocytes and triggering a cascade of intracellular signals that influence cell differentiation [11,23,34]. In vitro studies have shown that melatonin can inhibit the differentiation of preadipocytes by downregulating the expression of key adipogenic transcription factors, such as peroxisome proliferator-activated receptor gamma (PPARγ) and CCAAT/enhancer-binding protein alpha (C/EBPα), which are critical for the initiation and maintenance of the adipogenic pro-
gram (Table 1) [11,23,30,34]. The antiadipogenic effect of melatonin is also thought to involve the modulation of the signaling pathways such as the Wnt/β-catenin pathway, which plays a pivotal role in maintaining preadipocytes in an undifferentiated state [34,35]. By activating this pathway, melatonin may contribute to the inhibition of adipocyte differentiation.

Melatonin affects lipid metabolism within adipocytes, including the enzymes responsible for lipogenesis and lipolysis [22,23], the processes of fat formation and breakdown, respectively. Studies suggest that melatonin may reduce the activity of lipogenic enzymes, resulting in decreased triglyceride uptake and synthesis within adipocytes [22]. In addition, the role of melatonin as a regulator of circadian rhythms is also relevant to adiposity [30,33]. By maintaining proper circadian function, melatonin helps synchronize metabolic processes, including those related to energy expenditure and fat storage. Further human studies are necessary to confirm the efficacy and safety of melatonin in modulating adipocyte differentiation and fat accumulation. Additionally, it is important to understand the appropriate dosage and timing of administration.

The Effect of Melatonin in Adipose Mesenchymal Stem Cells

Adipose-derived mesenchymal stem cells (AMSCs) are multipotent stem cells derived from adipose tissue, the body’s storage of fat. They have gained attention in the scientific community for their potential in regenerative medicine. Under certain conditions, AMSCs can differentiate into various cell types, including adipocytes, osteoblasts, chondrocytes, myocytes, and potentially other cell types [32]. The important role of AMSCs in tissue regeneration has been emphasized by a significant amount of evidence, positioning them as a promising therapeutic option [31,32].

Melatonin has been found to enhance the adipogenic differentiation of mesenchymal stem cells (MSCs) by increasing key transcription factors such as PPARγ and C/EBPα [11,17]. It influences adipogenesis by regulating the expression of key adipocyte marker genes such as adiponectin and leptin, which are important for the terminal differentiation and functional maturation of adipocytes derived from MSCs [36]. Additionally, it exhibits anti-proliferative effects on adipose MSCs, modulating cell cycle progression [35].

Melatonin has been shown to reduce cellular senescence in MSCs and preserve their functionality and regenerative potential. It also has anti-inflammatory effects on adipose MSCs by suppressing the release of pro-inflammatory cytokines, which is important for creating a conducive microenvironment for regenerative processes [16,37,38]. Melatonin affects signaling pathways such as nuclear factor-kappa B (NF-κB) and mitogen-activated protein kinase (MAPK), by inhibiting their activation and reducing inflammation within the MSC niche [29,34]. Additionally, melatonin enhances the angiogenic potential of adipose MSCs by upregulating genes associated with angiogenesis, which contributes to improved vascularization in regenerating tissues [39]. It influences the signaling pathways of vascular endothelial growth factor (VEGF) and fibroblast growth factor 2 (FGF2), promoting angiogenesis and facilitating the integration of transplanted MSCs into damaged tissues [39].

The cellular responses to melatonin are mediated by the presence of melatonin receptors, particularly MT1 and MT2, on adipose MSCs [12,29]. The observed effects are orchestrated by intracellular signaling cascades by receptor activation. These findings not only enhance our understanding of cellular dynamics but also provide opportunities for improving the therapeutic potential of adipose MSCs in regenerative medicine. This highlights the significance of melatonin as a crucial regulator in cellular therapy [11].

Modulation of Lipid Metabolism Enzymes and Transport Proteins

Melatonin has been increasingly implicated in the modulation of lipid metabolism enzymes and transport proteins in humans [34,36]. This association is of great interest due to the critical role that lipid metabolism plays in overall metabolic health and disease [9,16]. The effect of melatonin on lipid metabolism can be observed through its interaction with various enzymes and transport proteins that are essential to lipid homeostasis. The hormone has been found to exert influence both directly and indirectly, through various signaling pathways and receptor-mediated mechanisms [33]. One of the primary enzymes in cholesterol biosynthesis is hydroxymethylglutaryl-CoA reductase (HMG-CoA reductase). Melatonin inhibits the activity of this enzyme, possibly through its antioxidant properties or through melatonin receptors expressed in the liver [40]. It may lower the synthesis of cholesterol by reducing the activity of HMG-CoA reductase, which can have a favorable impact on lipid profiles [40,41]. Additionally, melatonin targets lipoprotein lipase (LPL), a key enzyme responsible for the hydrolysis of triglycerides in the bloodstream, facilitating their uptake by fat and muscle tissue [29,42]. Previous studies have suggested that melatonin may enhance LPL activity, which potentially reduces the risk of atherosclerosis and cardiovascular disease by accelerating the clearance of triglycerides from the plasma [10,26,43].

Melatonin is thought to interact with adipocytes, affecting the expression and function of proteins involved in fatty acid uptake and storage along the lipid metabolism pathway [19,23]. This passage discusses the downregulation of transport proteins such as fatty acid transport protein (FATP), and the promotion of pathways that favor lipid mobilization over storage, thereby possibly contributing to a reduction in visceral fat accumulation [42,44,45]. It may encourage the use of fatty acids as an energy source by influencing these enzymes, rather than storing them as body fat. The role of melatonin as an antioxidant is well-documented, providing protection against lipid peroxidation.
This process occurs when free radicals attack lipids, leading to cell damage and contributing to the development of atherosclerosis [19,40,43]. Through its ability to scavenge free radicals, melatonin may help maintain the lipid integrity and reduce oxidative stress on the cardiovascular system.

In summary, the influence of melatonin on lipid metabolism enzymes and transport proteins suggests its potential role in regulating lipid homeostasis in humans. Although the underlying mechanisms are becoming clearer, further investigation is required to translate these effects into clinical practice. Further research, particularly randomized controlled trials, is necessary to gain a better understanding of the therapeutic potential of melatonin in lipid metabolism and its potential benefits for metabolic health.

The Effect of Melatonin on Regulation of Body Weight and Obesity

It has been suggested that melatonin plays a role in regulating body weight and obesity. Extensive research has been conducted into potential regulatory mechanisms and treatments for obesity, with melatonin emerging as an area of particular interest. The regulation of body weight is primarily determined by energy balance, which may be influenced by melatonin through its effects on both energy intake and expenditure. Melatonin is thought to activate brown adipose tissue (BAT), which is responsible for thermogenesis, the process of heat production in organisms (Table 2) [11,23]. This activation is thought to stimulate energy expenditure by increasing the expression of uncoupling proteins, such as UCP1 (Table 1), which enhances the thermogenic capacity of BAT [24,46]. This increased thermogenesis has the potential to counteract obesity. Recently, interesting studies also suggest that melatonin may enhance BAT activity, promoting thermogenesis and energy expenditure [18,46]. These findings open exciting avenues for exploring the potential role of melatonin in managing obesity and associated metabolic disorders. Nevertheless, melatonin induces hypothermia by modulating thermoregulatory centers in the brain during sleep. These contrasting effects may arise from different mechanisms and contexts (acute exposure versus circadian rhythms), reflecting the multifaced roles of melatonin. Consequently, further mechanistic data is required to elucidate these conflicting functions.

Appetite regulation is a complex process that involves multiple hormones signaling hunger and fullness to the brain [36,47]. Melatonin interacts with hormonal pathways, including those involving leptin and ghrelin [47]. By modulating the secretion and action of these hormones, melatonin could influence appe-

<table>
<thead>
<tr>
<th>Feature</th>
<th>White adipose tissue (WAT)</th>
<th>Beige fat</th>
<th>Brown adipose tissue (BAT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main function</td>
<td>Stores excess calories in the form of triglycerides for later use by the body; main type of fat accumulating in obesity</td>
<td>Displays functional flexibility between energy expenditure and storage depending on stimuli</td>
<td>Specialized in burning calories to produce heat (thermogenesis); helps maintain body temperature in cold</td>
</tr>
<tr>
<td>Cell color</td>
<td>Large, unilocular white lipid droplet gives cells a white appearance</td>
<td>Heterogeneous cell appearance ranging from white to brown representing intermediate phenotype</td>
<td>Brown coloration due to high mitochondrial content and increased vascularity</td>
</tr>
<tr>
<td>Location in human body</td>
<td>Subcutaneous tissue throughout the body, concentrated around thighs, hips and abdomen; visceral deposition around organs associated with metabolic dysfunction risk</td>
<td>Interspersed within some white adipose depots like subcutaneous fat</td>
<td>Concentrated in areas like supravacular, paravertebral, suprarenal regions</td>
</tr>
<tr>
<td>Mitochondrial density</td>
<td>Low number of mitochondria dedicated more to lipid storage over oxidation</td>
<td>Moderate mitochondrial density with some oxidative capacity</td>
<td>Very high mitochondrial density to drive thermogenesis</td>
</tr>
<tr>
<td>Lipid droplet size</td>
<td>Single large lipid droplet occupying 90% of cell volume</td>
<td>Multiple small and medium-sized lipid droplets</td>
<td>Multiple tiny lipid droplets dispersed between mitochondria</td>
</tr>
<tr>
<td>Key protein markers</td>
<td>Expresses high levels of genes like leptin, adiponectin and PPARγ</td>
<td>Variable co-expression of beige markers like UCP1, CITED1 along with white markers</td>
<td>High UCP1, CITED1; low leptin and adiponectin</td>
</tr>
<tr>
<td>Response to cold exposure or β-adrenergic stimulation</td>
<td>Does not directly respond</td>
<td>Activates thermogenic program - increases oxidation, heat production and UCP1</td>
<td>Markedly activates thermogenesis program and fat burning</td>
</tr>
</tbody>
</table>

PPARγ, peroxisome proliferator-activated receptor gamma; UCP1, uncoupling protein 1; CITED1, Cbp/p300-interacting transactivator with Glu/Asp-rich carboxy-terminal domain 1.
tite and food intake, playing a role in controlling body weight. However, the findings are heterogeneous and do not allow for a robust conclusion [47].

**The Effect of Melatonin on Glucose and Lipid Metabolism by Circadian Rhythm**

The role of melatonin in maintaining circadian rhythms is also crucial for metabolic processes, which follow a diurnal pattern [33]. Circadian misalignment, which is often observed in shift workers and individuals with irregular sleep patterns, has been linked to metabolic dysregulation and obesity [30,33,47]. By realigning disrupted circadian rhythms, melatonin may help normalize metabolic rates and support weight regulation. Multiple population studies have shown that there is a negative correlation between circulating blood melatonin concentrations and measures of adiposity, such as body mass index (BMI) and abdominal obesity [48,49]. Additionally, obese individuals were also found to have lower levels of melatonin compared to non-obese matched controls [10,49,50]. Disruption of melatonin circadian rhythms, such as in nighttime shift work and social jet lag, has also been associated with increased adiposity [51,52]. These epidemiological data link impaired melatonin status to the development of an obese phenotype. Based on the correlational data presented above, the potential of melatonin supplementation to combat obesity has been extensively studied in rodent models over the past two decades [19,41,45]. In various studies conducted on mice and rats with diet-induced obesity, melatonin administration consistently prevented a 15%–30% increase in body weight and completely inhibited visceral fat accumulation, even when a high-fat diet was consumed [17,45,53]. Although animal studies have shown that exogenous melatonin is effective against obesity, its translation to human clinical trials has been limited so far. Several preliminary studies have examined the effects of oral melatonin supplements on body weight and composition in overweight adults or various obese phenotypes [17,23,36]. However, it is important to note that these studies are preliminary, and further research is needed to determine the efficacy of melatonin supplementation in treating obesity in humans. Moreover, future studies should focus on the long-term effects of melatonin, exploring individual variability in response to melatonin, and examining its potential use in combination with lifestyle interventions for the prevention and management of obesity.

**Melatonin and Oxidative Stress/Inflammation in Metabolic Disorders**

Melatonin has been shown to have multiple effects on inflammation, oxidative stress caused by reactive oxygen species (ROS), and metabolic disorders in humans (Table 1) [10,23]. Its significant antioxidant capabilities are demonstrated by its ability to directly scavenge ROS and increase the expression of antioxidant enzymes, thereby reducing oxidative stress, which is a contributing factor in the development of various metabolic disorders [16,24,33]. Inflammation is a common factor that links several metabolic disorders, such as obesity, diabetes, and cardiovascular diseases [3,17,54]. Melatonin’s anti-inflammatory effects are mediated by inhibiting the NF-κB pathway, which is central to the inflammatory response [16]. By modulating this pathway, melatonin can reduce the secretion of pro-inflammatory cytokines, thereby mitigating the inflammatory state associated with metabolic dysregulation. Oxidative stress and chronic inflammation are widely recognized as key contributors to the pathogenesis of metabolic disorders [3]. Therefore, potential therapeutic interventions have gained increased attention [3,13,54]. Melatonin is widely known for its potent antioxidant properties, which play a crucial role in the body’s defense against oxidative stress [22,24]. This state is characterized by an imbalance between the production of harmful free radicals and the ability to counteract their harmful effects in the human body. The antioxidant function of melatonin is attributed to its chemical structure, specifically the indole ring [22,26], which enables direct scavenging of a wide range of reactive oxygen and nitrogen species. Melatonin is unique among other antioxidants because of its ability to easily cross physiological barriers, such as the blood-brain barrier, due to its amphiphilic nature. This property allows it to reach all cells and protect them from oxidative damage [26]. Furthermore, melatonin acts as a free radical scavenger. It also exerts antioxidant effects indirectly by stimulating the expression of antioxidant enzymes, such as superoxide dismutase, catalase, and glutathione peroxidase [15]. To improve cellular defense mechanisms against oxidative stress, it is important to maintain mitochondrial function [14]. Melatonin present in mitochondria can help reduce oxidative harm, stabilize the electron transport chain, and maintain cellular energy balance [17,33]. The potent antioxidant properties of melatonin make it a crucial defender against oxidative stress in metabolic disorders such as type 2 diabetes and obesity, where elevated oxidative stress contributes to insulin resistance and impaired metabolic function [23,45,53].

Melatonin regulates various signaling pathways, including NF-κB, transforming growth factor-β (TGF-β), and MAPK, which are pivotal players in inflammation [16,55]. By inhibiting their activation, melatonin downregulates the expression of various pro-inflammatory cytokines [16]. Furthermore, recent studies have shown that melatonin also suppresses inflammasome activation, a crucial mediator of inflammation, by down-regulating NLRP3 inflammasome components, thereby reducing the release of interleukin-1β (IL-1β) and interleukin-18 (IL-18) [16,56].

**The Role of Melatonin in Metabolic Inflammation**

Metabolic inflammation, also known as meta-inflammation, is a chronic low-grade inflammation that is associated with metabolic dysregulation and obesity in the human body [4,54]. Mel-
Melatonin, a hormone that influences various cellular and molecular pathways, plays a significant role in regulating metabolic inflammation (Table 3) [23,33,56]. At the cellular level, melatonin influences the behavior of immune cells central to the inflammatory response. It regulates adhesion molecules to impede leukocyte adhesion to vascular endothelial cells [39,57]. This inhibits the recruitment of immune cells to sites of inflammation, mitigating the inflammatory response. Additionally, it downregulates the expression of pro-inflammatory cytokines, including tumor necrosis factor alpha (TNF-α) and interleukins, which mitigates the chronic low-grade inflammation observed in metabolic disorders. This anti-inflammatory action is crucial for addressing the systemic inflammation linked to insulin resistance and metabolic dysfunction. Macrophages have a crucial role in controlling immune and inflammatory reactions [58]. They can polarize into two types: the classically pro-inflammatory M1 phenotype or the alternatively anti-inflammatory M2 phenotype. The imbalance between these M1/M2 activation states is often the cause of many chronic inflammatory diseases [16,59]. Melatonin has the potential to modulate macrophage polarization, which could have therapeutic implications. Recent studies suggest that melatonin may inhibit the activation of M1 macrophages and promote the M2 phenotype [56,59]. In lipopolysaccharide (LPS)-stimulated macrophages, melatonin suppresses the expression of M1 marker genes, including TNF-α, IL-1β, iNOS, and COX-2. This is achieved through the inhibition of NF-κB signaling, a key pathway driving M1 activation [59,60]. Additionally, melatonin upregulates M2 macrophage markers such as Arg-1, IL-10, and CD206 [59,61] and also activates STAT6 to induce M2 polarization and inhibits STAT1 involved in M1 progression [59]. Thus, as described above, these immunomodulatory effects of melatonin on macrophage phenotypes have generated interest in its potential therapeutic use for inflammatory diseases. For example, melatonin treatment has been shown to suppress endothelial inflammation and atherosclerosis development in animal models, which is associated with an increase in anti-inflammatory M2 macrophages in plaques [62,63].

Melatonin also modulates T-cell responses in the context of metabolic disorders [64]. T cells are a crucial component of the adaptive immune system and can be classified into subsets, including Th1, Th2, Th17, and regulatory T cells (Tregs), each with unique functions and cytokine production profiles. Th1 cells produce pro-inflammatory cytokines, such as interferon-gamma (IFN-γ), while Th2 cells produce anti-inflammatory cytokines, such as interleukin-4 (IL-4). Th17 cells are recognized to participate in autoimmune responses, while Tregs play a crucial role in maintaining immune tolerance and preventing autoimmunity. The balance of T helper cells, a type of T-cell crucial to immune response, can be specifically influenced by Th1 and Th2 cells. Th1 cells activate macrophages and promote cellular immunity, which is associated with inflammation. In contrast, Th2 cells promote humoral immunity, which is characterized by the production of antibodies and associated with anti-inflammatory responses. Metabolic disorders often involve an imbalance between Th1 and Th2 responses, with Th1 responses being overly dominant. Therefore, this imbalance results in increased metabolic inflammation, which can exacerbate the disorder. In the context of obesity and its associated metabolic dysfunction, melatonin has been found to have a beneficial effect on dampening inflammatory T cell responses. Studies on mouse models of diet-induced obesity have shown that melatonin inhibits the activation and proliferative capacity of both CD4+ and CD8+ T cells, resulting in an overall reduction in T cell-mediated inflammation in adipose tissue and circulation [54,65]. In addition, melatonin reduces the production of pro-inflammatory cytokines IFNγ and IL-17 from CD4+ T helper cell subsets Th1 and Th17. These cytokines are responsible for the inflammatory responses that lead to insulin resistance in metabolic disease [16,54,66]. On the other hand, melatonin promotes the production of the anti-inflammatory cytokine IL-10 by regulatory T cells, which helps

### Table 3. The key functions of melatonin in regulating metabolic inflammation

<table>
<thead>
<tr>
<th>Function</th>
<th>Description</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibits immune cell recruitment</td>
<td>Impedes leukocyte adhesion to endothelial cells by modulating adhesion molecules</td>
<td>[39,56]</td>
</tr>
<tr>
<td>Downregulates pro-inflammatory cytokines</td>
<td>Reduces release of TNF-α, IL-1β, IL-6, and other inflammatory mediators</td>
<td>[29,54,58,59]</td>
</tr>
<tr>
<td>Promotes M2 macrophage polarization</td>
<td>Activates STAT6 pathway and inhibits STAT1; shifts balance from inflammatory M1 to anti-inflammatory M2 phenotype</td>
<td>[58,60]</td>
</tr>
<tr>
<td>Suppresses inflammasome activation</td>
<td>Downregulates NLRP3 components to reduce IL-1β and IL-18 production</td>
<td>[29,55]</td>
</tr>
<tr>
<td>Attenuates T cell-mediated inflammation</td>
<td>Lowers inflammatory cytokine (IFNγ and IL-17) from Th1 and Th17 cells; increases anti-inflammatory IL-10 from Tregs</td>
<td>[29,53,63-65]</td>
</tr>
<tr>
<td>Exerts antioxidant effects</td>
<td>Scavenges ROS and upregulates antioxidant enzymes, reducing oxidative damage that drives inflammation</td>
<td>[15,25,33]</td>
</tr>
</tbody>
</table>

TNF-α, tumor necrosis factor alpha; IL-1β, interleukin 1 beta; IL-6, interleukin 6; STAT6, signal transducer and activator of transcription 6; STAT1, signal transducer and activator of transcription 1; NLRP3, NLR family pyrin domain containing 3; IL-18, interleukin 18; IFNγ, interferon gamma; IL-17, interleukin 17; Th1, T helper 1; Th17, T helper 17; IL-10, interleukin 10; Tregs, regulatory T cells; ROS, reactive oxygen species.
to suppress excessive inflammation [16,59]. Melatonin may modulate T lymphocytes by interfering with their signaling pathways, particularly the metabolic sensor mammalian target of rapamycin (mTOR) kinase [66]. The effect of melatonin on metabolic inflammation has produced inconsistent results in clinical studies. Several studies have shown beneficial effects on inflammatory markers, while others have shown minimal impact [66]. Further research is needed to optimize the dosage, timing, and understand the long-term effects of melatonin supplementation. Melatonin has potential therapeutic applications in managing metabolic inflammation due to its effects on immune cells, inflammatory pathways, antioxidant defense, and mitochondrial protection. However, translating these findings into clinical practice requires a more comprehensive and targeted approach.

CONCLUSION

In this review, we examined the growing evidence supporting the important role of the pleiotropic indoleamine melatonin in metabolic regulation and dysfunction. Mechanistic data demonstrated the intricate involvement of melatonin signaling in maintaining glucose and lipid homeostasis, attenuating oxidative stress and inflammation. Melatonin is considered an endogenous buffer against metabolic perturbations that drive pathogenesis of prevalent cardiometabolic disorders such as obesity, diabetes, and atherosclerotic cardiovascular disease. Promising preclinical findings suggested that melatonin supplementation could be a potential adjuvant treatment for various facets of metabolic disease. However, large-scale, rigorous human trials are needed to validate this therapeutic potential. Establishing clinical efficacy and practical application of melatonin will require optimizing dosing, timing of administration, and assessing long-term impacts. The excellent safety profile and accessibility of melatonin make it a promising candidate for combating the global crisis of metabolic dysfunction in a safe, affordable, and sustainable manner, reducing associated morbidity and socioeconomic burdens. In conclusion, utilizing melatonin as a therapeutic approach represents a shift towards holistic methods for addressing complex diseases. Its multifunctional properties, including metabolic regulation, anti-inflammatory effects, and antioxidant activity, make it a promising candidate for managing current public health challenges. Well-designed trials are needed to fully harness its potential.

Availability of Data and Material
Data sharing not applicable to this article as no datasets were generated or analyzed during the study.

Author Contributions
Conceptualization: Jinkwan Kim. Data curation: Seok Hyun Hong, Jinkwan Kim. Writing—original draft: Seok Hyun Hong, Jinkwan Kim. Writing—review & editing: Seok Hyun Hong, Jinkwan Kim.

Conflicts of Interest
The authors have no potential conflicts of interest to disclose.

Funding Statement
This study was supported by a fund from the National Research Foundation of Korea (Grant No. NRF-2021R1F1A1063264).

Acknowledgements
None

REFERENCES
18. Fernández Vázquez G, Reiter RJ, Agúl A. Melatonin increases brown adipose tissue mass and function in Zucker diabetic fatty rats: implica-
Melatonin and Metabolic Dysfunction
Hong SH and Kim J


40. Ou TH, Tung YT, Yang TH, Chien YW. Melatonin improves fatty liver syndrome by inhibiting the lipogenesis pathway in hamsters with high-fat diet-induced hyperlipidemia. *Nutrients* 2019; 11:748.


