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REVIEW

The Warburg Effect Beyond Cancer: Melatonin as a Metabolic Modulator in Non-Neoplastic Disorders

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ABSTRACT: Aerobic glycolysis, also known as the Warburg effect, and the accumulation of lactate that it causes, are increasingly recognized outside the field of oncology as triggers of chronic non-neoplastic disorders. This review integrates preclinical and clinical evidence to evaluate the ability of melatonin to reverse Warburg-effect-like metabolic reprogramming. Literature on neurodegeneration, age-related sarcopenia, type 2 diabetes, chronic kidney disease, heart failure and pulmonary arterial hypertension (PAH) has been reviewed and synthesised. In all of these conditions, hypoxia-inducible factor 1α (HIF-1α) and pyruvate dehydrogenase kinase 4 (PDK4) inhibit the pyruvate dehydrogenase complex. This diverts pyruvate away from the tricarboxylic acid (TCA) cycle and promotes glycolysis. In cell and animal models, melatonin consistently inhibits PDK4, destabilizes HIF-1α under normoxic conditions, activates SIRT1/3-dependent mitochondrial biogenesis and mitophagy, and eliminates reactive oxygen and nitrogen species. These actions reduce lactate production, restore oxidative phosphorylation and attenuate tissue damage. This appears to induce cognitive and synaptic improvements in Alzheimer's and Parkinson's disease models, increased muscle mass and function in ageing rodents, improved insulin sensitivity alongside suppression of hepatic gluconeogenesis in diabetic models, reduced fibrosis in nephropathy,and normalization of vascular remodeling in hypoxia-induced pulmonary arterial hypertension (PAH). Early-stage clinical trials corroborate a decrease in oxidative and inflammatory markers, improved sleep quality and modest cognitive benefits. However, they report conflicting effects on insulin sensitivity, which are largely related to the dose and timing of administration in relation to food intake. Overall, the current data suggest that melatonin is a pleiotropic metabolic modulator capable of counteracting the Warburg phenotype in multiple organs. However, human studies remain scarce, and well-designed randomised trials incorporating chronotherapy are needed before clinical adoption.

KEYWORDS: Neurodegenerative diseases; ageing-related conditions; metabolic disorders; pyruvate dehydrogenase; free radicals; glucose processing

1 Introduction

The Warburg effect, originally described by Otto Warburg in the 1920s [1], represents a metabolic phenomenon in which cells prioritize aerobic glycolysis over mitochondrial oxidative phosphorylation, even in the presence of oxygen. This metabolic shift, involving increased lactate production and reduced energy production, was initially identified as a hallmark of tumour metabolism. However, recent research

has revealed that this phenomenon is not unique to cancer but is also observed in various non-neoplastic pathologies [2,3].

Under normal conditions, pyruvate generated during glycolysis enters the mitochondria to be metabolised in the Krebs cycle and subsequently used in the electron transport chain to produce ATP by oxidative phosphorylation. This process generates up to 36 molecules of ATP per molecule of metabolised glucose. In contrast, the Warburg effect is characterised by a diversion of pyruvate to lactic fermentation in the cytosol, resulting in the production of only 2 molecules of ATP per glucose. Although this pathway is less energy efficient, it provides adaptive advantages to cells under stress conditions. These advantages include rapid energy generation and production of biosynthetic intermediates necessary for cell growth [4,5] (Fig. 1).

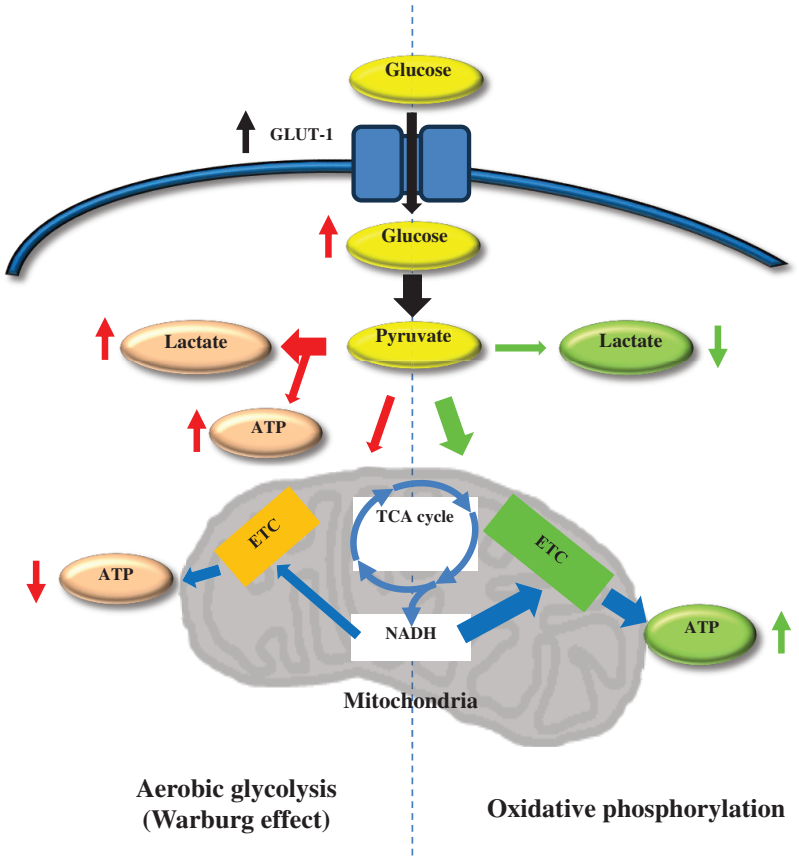

Figure 1: Schematic representation of the differences between oxidative phosphorylation and aerobic glycolysis (Warburg effect). Glut-1, glucose transporter; TCA cycle, tricarboxiylic acid cycle; etc., electron transport chain

In the context of cancer, the Warburg effect facilitates cell proliferation by providing precursors for nucleotide, lipid and protein synthesis. In addition, it reduces the generation of reactive oxygen species (ROS) derived from mitochondrial activity, protecting tumour cells from oxidative damage. It also contributes to an acidic microenvironment due to lactate accumulation, which favours tumour invasion and immune evasion [6,7]. These features have been extensively studied and clinically exploited by diagnostic tools such as 18F-fluorodeoxyglucose (FDG)-based positron emission tomography (PET), which detects increased glucose uptake by tumour cells [8].

Although the Warburg effect was initially thought to be a direct consequence of mitochondrial dysfunction in cancer cells, subsequent studies have shown that this phenomenon can be induced by external

factors such as hypoxia or chronic inflammation. In particular, hypoxia-inducible factor 1-alpha (HIF-1α) plays a central role by promoting the expression of glycolysis-related genes and suppressing genes involved in oxidative phosphorylation [9,10]. HIF-1α activation can occur even under normoxic conditions due to inflammatory stimuli or persistent oxidative stress, extending the scope of the Warburg effect beyond cancer to other pathologies. In addition, upregulation of pyruvate dehydrogenase kinase 4 (PDK4) inhibits the pyruvate dehydrogenase complex, diverting pyruvate to lactate and attenuating oxidative phosphorylation, while immunometabolic signaling further sustains this glycolytic shift under normoxia [2,3,11].

Melatonin is a multifunctional molecule with wide-range biological effects (Fig. 2). Although traditionally associated with circadian regulation, it has also emerged as a key modulator of cellular metabolism and mitochondrial protector. Although historically its synthesis was thought to occur primarily in the pineal gland at night, current evidence supports extrapineal synthesis of melatonin with mitochondrial participation across multiple tissues and selective mitochondrial accumulation via transporters; however, the exact proportion relative to the whole-body pool remains uncertain and is likely tissue- and species-dependent [12,13]. This intramitochondrial melatonin acts locally as an essential metabolic regulator and antioxidant, with concentrations up to 100 times higher in mitochondria than in blood plasma [12].

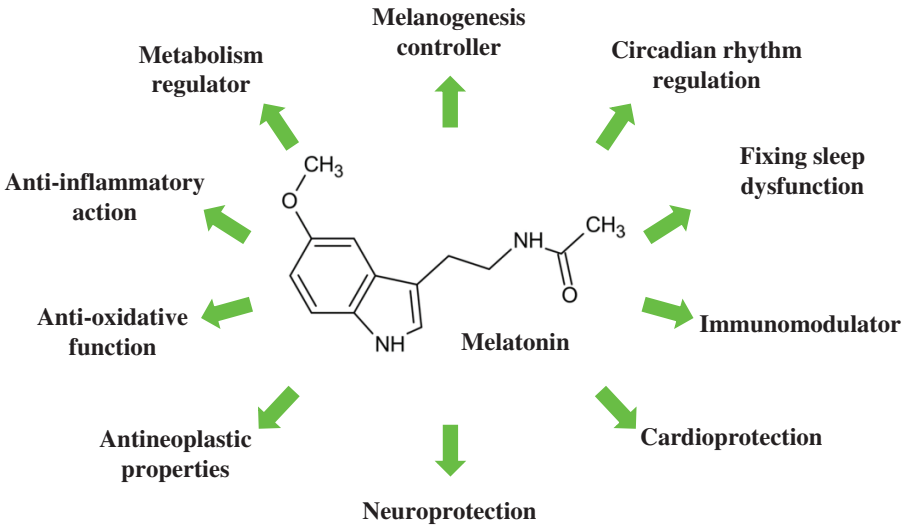

Figure 2: Schematic representation of biological effects of melatonin

Melatonin possesses unique properties as a direct and indirect antioxidant. It neutralises highly ROS such as hydroxyl radical (OH) and peroxynitrite ($ONOO^-$) through direct chemical reactions [14]. In addition, it stimulates endogenous antioxidant systems by increasing the activity of enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GPx) and catalase (CAT) [14,15]. These actions protect mitochondria from oxidative damage and maintain their functionality under adverse conditions, even in situations of severe oxidative stress such as ischaemia/reperfusion [14]. Its ability to cross cell membranes and selectively accumulate in mitochondria, thanks to specific transporters such as human peptide transporter (PEPT) 1/2, allows it to reach critical therapeutic concentrations in these organelles [12,16].

In addition to its antioxidant properties, melatonin plays a crucial role in regulating cellular energy metabolism. It acts by inhibiting pyruvate dehydrogenase kinases (PDKs), which are responsible for inactivating the pyruvate dehydrogenase (PDH) complex, thus allowing pyruvate to enter the Krebs cycle and be used to generate ATP via oxidative phosphorylation [13,17]. In addition, it positively regulates sirtuins such as SIRT3, a mitochondrial NAD+-dependent deacetylase that improves metabolic efficiency and reduces

intracellular oxidative stress by deacetylating and activating enzymes such as SOD2 [15,16]. In experimental models, these actions reprogram cellular metabolism from a glycolytic to a more oxidative state, effectively counteracting the Warburg effect in both cancer and neurodegenerative diseases [11,13,17,18].

The relationship between melatonin and the Warburg effect is bidirectional: while low melatonin levels favour this aberrant metabolic phenotype, melatonin supplementation can reverse it. For example, in models of Alzheimer's disease (AD), where β-amyloid deposits induce an exacerbated glycolytic state, administration of melatonin significantly reduces intracellular lactate levels and restores critical mitochondrial functions, such as respiratory chain complex IV activity [19,20]. These effects are mediated by melatonin's ability to suppress HIF-1α, a master regulator of glycolytic genes, and reactivate mitochondrial oxidative phosphorylation [17].

This paper provides a critical review of the molecular mechanisms by which melatonin modulates the Warburg effect in non-neoplastic diseases grouped into three broad categories: neurodegenerative diseases, ageing-related conditions, and metabolic disorders. The findings reviewed demonstrate that the Warburg effect is not exclusive to cancerous processes but is also implicated in various pathologies characterised by mitochondria-centred metabolic alterations. In this context, the ability of melatonin to neutralise, slow down, and even correct these dysfunctions is particularly relevant, given that these processes are widely distributed in human pathophysiology. In this review, we examine three interconnected aspects for every condition: the metabolic underpinnings of the Warburg effect, the influence of antioxidant and energy metabolism-regulating actions of melatonin, and the specific therapeutic applications. By integrating recent preclinical and clinical evidence, this work seeks to establish a solid basis for future research aimed at developing melatonin-based therapeutic strategies for pathologies with metabolic dysfunction.

2 Neurodegenerative Diseases: Warburg Metabolism and Neuroprotective Effects of Melatonin

2.1 Alzheimer's Disease: Warburg-Type Metabolic Reprogramming

AD is characterised by a metabolic shift towards aerobic glycolysis, similar to the Warburg effect described in tumour cells. 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) studies have consistently demonstrated a decrease in glucose oxidation in temporal and parietal brain regions of AD patients, even in pre-symptomatic stages, reflecting an early energy deficit. This metabolic shift involves increased glycolytic flux and elevated lactate production, suggesting a diversion of pyruvate to lactate fermentation instead of the Krebs cycle [21].

At the molecular level, this metabolic reprogramming is driven by hyperactivation of pyruvate dehydrogenase kinase (PDK4), which inhibits the pyruvate dehydrogenase (PDH) complex, and by overexpression of lactate dehydrogenase A (LDH-A), which promotes lactate production even under normoxic conditions [22,23]. Amyloid-beta (Aβ) oligomers aggravate this dysfunction by stabilizing HIF-1α thereby promoting the expression of glycolytic genes such as glucose transporter (GLUT)1 and PDK4, perpetuating neuronal oxidative and energetic stress [21,24]. In Alzheimer's disease, these actions are expected to counter Warburg-like reprogramming by tempering HIF-1α signaling, lowering PDK4 and thereby relieving PDH inhibition, and upregulating SIRT3/PGC-1α to enhance complex IV function—mechanisms that together reduce lactate accumulation and favor oxidative phosphorylation.

In the context of this disease, melatonin has been shown to modulate the altered energy metabolism associated with the Warburg effect. Preclinical studies have shown that melatonin administration improves mitochondrial function by increasing respiratory chain complex IV activity and promoting mitochondrial biogenesis through the activation of PGC-1α, a master regulator of energy homeostasis [25,26]. Studies in AD transgenic mice have confirmed that melatonin not only attenuates β-amyloid accumulation and

Tau hyperphosphorylation, but also restores mitochondrial autophagy and reduces neuroinflammation, key mechanisms in disease progression [27]. However, extrapolation of these effects to humans requires rigorous clinical trials assessing specific metabolic parameters (lactate, PDK4) and their relationship with cognitive improvement.

2.2 Parkinson's Disease: Compensatory Glycolysis and Dopaminergic Vulnerability

In Parkinson's disease (PD), affected dopaminergic neurons show a metabolic pattern similar to the Warburg effect. Mitochondrial complex I deficiency triggers a compensatory dependence on aerobic glycolysis. This metabolic shift includes increased GLUT3-mediated glucose uptake, increased mitochondrial membrane-bound hexokinase-II activity, and elevated lactate accumulation due to LDH-A hyperactivity [28]. Oligomeric alpha-synuclein aggravates this mitochondrial dysfunction by interfering with critical processes such as mitochondrial dynamics and mitophagy, perpetuating neuronal energy stress [29,30].

Melatonin has also shown promising effects in PD. In 1-metil-4-fenil,6-tetrahidropiridina (MPTP)- or rotenone-induced models, this compound protects against dopaminergic degeneration by several complementary mechanisms [31]. First, it prevents inhibition of mitochondrial complex I and significantly reduces intracellular levels of ROS [14,32]. Second, it stabilises respiratory complexes II–IV, improving both mitochondrial transmembrane potential and ATP synthesis [33]. Third, it directly reduces toxic aggregation of oligomeric alpha-synuclein, preserving neuronal bioenergetic functions [34]. In animal models treated with melatonin, preservation of affected dopaminergic neurons and a significant improvement in motor parameters have been observed [35,36].

2.3 Other Neurodegenerative Diseases: Warburg Effect and the Role of Melatonin

Although, within neurodegenerative diseases, the Warburg effect as such has been described exclusively in AD and PD, metabolic alterations involving mitochondria, whether or not related to melatonin, have been documented in other neurodegenerative diseases, such as Huntington's disease (HD), amyotrophic lateral sclerosis (ALS) and multiple sclerosis (MS), as well as in conditions associated with chronic cerebral hypoperfusion. These findings broaden the spectrum of pathologies where metabolic reprogramming and melatonin play critical roles and we believe they should not be excluded from this review if we are to give a true picture of the extent of this effect.

In HD, characterised by the accumulation of mutant huntingtin, a significant reduction in plasma melatonin levels has been observed, correlated with sleep disturbances and circadian disruption [37]. The Warburg effect in HD has also been directly studied, mitochondrial dysfunction and oxidative stress are prominent features [38]. Studies in animal models suggest that melatonin may mitigate these defects by improving the efficiency of complex I of the respiratory chain and reducing the production of ROS, mechanisms that may indirectly counteract aberrant glycolytic metabolism [39].

In ALS, where motor neurons undergo progressive degeneration, melatonin has been shown to induce autophagy by activating SIRT1, a mitochondrial deacetylase that enhances the removal of protein aggregates and restores energy homeostasis [40]. In murine models of ALS, melatonin administration increased Beclin-1 expression and LC3II/LC3I ratio, key markers of autophagy, while reducing p62 accumulation, suggesting a restoration of mitochondrial function and a possible correction of the glycolytic bias [40].

In the context of chronic cerebral hypoperfusion associated with vascular cognitive impairment, melatonin has shown protective effects by modulating energy metabolism and reducing oxidative stress. In mouse models of carotid artery stenosis-induced hypoperfusion, melatonin improved white matter integrity

and reduced the expression of proinflammatory cytokines (TNF-α, IL-1β) and oxidative stress markers (MDA, 8-OHdG), with some of the effects being mediated partly through the MT2 receptor [7,41].

In MS, a demyelinating disease with a prominent inflammatory component, melatonin has been shown to modulate the Th17/Th1 response and reduce levels of proinflammatory cytokines (IL-6, IL-17) in patients with the relapsing-remitting form [42]. Although the direct link to the Warburg effect has not been explored, mitochondrial dysfunction in oligodendrocytes and neurons is a pathogenic hallmark in MS. Preclinical studies indicate that melatonin enhances the activity of antioxidant enzymes (superoxide dismutase, glutathione peroxidase) and reduces NLRP3 inflammasome activation, which could counteract the metabolic stress associated with aerobic glycolysis [42].

The cerebral consequences of non-neurological diseases must also be considered. The harmful effects that obesity can induce at the cerebral level has been carefully studied, given the metabolic stress it causes at the glycolytic level in this organ [43,44]. Thus, a decrease in brain volume in obese animals, followed by patterns of alterations like those previously described in other pathologies, are observed. These alterations include deregulation of inflammation, endoplasmic reticulum dysfunction with accumulation of misfolded proteins, and overexpressed but not sufficiently effective autophagy that does not prevent the formation of aggresomes, characteristic of multiple dementia processes [45]. This is accompanied by significant alterations in glucose metabolism in which the Warburg effect is evident. Melatonin is able to reverse this effect by acting on hexokinase II, while reducing circulating oxidative stress together with the production of misfolded proteins, thus reducing the need for autophagy and the production of aggresomes and thus their synergistic effect on other proteins. This would result in a significant improvement in the transmission of information [43,44].

These findings, although preliminary in some pathologies, underline the cross-cutting role of melatonin in modulating energy metabolism in neurodegenerative diseases. Future studies should further explore the direct measurement of markers such as lactate, PDK4, and PDH activity to confirm their impact on the Warburg effect in these contexts.

2.4 Clinical Evidence and Therapeutic Perspectives of Melatonin in Relation to the Warburg Effect in Neurodegenerative Diseases

Direct clinical evidence linking melatonin to modulation of the Warburg effect in neurodegenerative diseases is limited, but human studies support its therapeutic potential by improving clinical parameters associated with metabolic dysfunction. In AD, several clinical trials and meta-analyses have shown significant improvements in cognition and sleep quality following melatonin administration, especially in mild stages or in patients with mild cognitive impairment. For example, a recent meta-analysis including nine studies in AD patients concluded that melatonin treatment for more than 12 weeks significantly improves the Mini-Mental State Examination (MMSE) score, especially in early stages of the disease [46]. These results are reinforced by controlled clinical trials that have documented that melatonin administration improves both cognitive performance and depressive symptoms and stabilises the sleep-wake rhythm, although metabolic markers such as lactate or PDK4 were not directly measured [39]. Furthermore, in a multicentre, double-blind, placebo-controlled trial, the use of extended-release melatonin improved cognitive function and sleep efficiency in patients with mild to moderate AD, with more marked effects in those with comorbid insomnia [47]. Although specific metabolic markers of the Warburg effect were not assessed, the functional improvement and stabilisation of brain hypometabolism observed in neuroimaging studies suggest a possible restoration of underlying oxidative metabolism.

In PD, clinical evidence also points to benefits of melatonin on non-motor symptoms, especially sleep disturbances, which are closely linked to metabolic pathophysiology and neuroinflammation. A recent

meta-analysis of randomised controlled trials concluded that melatonin administration significantly improves motor symptoms and sleep quality in PD patients, according to the Unified Parkinson Disease Rating Scale (UPDRS) and the Pittsburgh Sleep Quality Index (PSQI) [48]. Other clinical trials have shown that melatonin improves REM sleep quality and reduces daytime sleepiness in patients with REM sleep behaviour disorder (RBD), a common precursor of PD [49]. In addition, longitudinal studies with extended-release melatonin have suggested stabilisation of dopamine transporter density in brain imaging, which may be related to the normalisation of neuronal energy metabolism [50].

Although human clinical trials have not explicitly evaluated the impact of melatonin on classical parameters of the Warburg effect, such as CSF lactate reduction or mitochondrial complex IV activity, the biological plausibility of its action is supported by preclinical studies and improvement in clinical parameters related to metabolic dysfunction. Furthermore, it has been proposed that chronotherapeutic administration of melatonin (nightly doses) optimises its brain bioavailability and synchronises its action with circadian rhythms of mitochondrial activity, which could be relevant in the reversal of aerobic glycolysis [51]. Finally, experimental strategies, including mitochondria-targeted nanoparticles designed to enhance brain exposure to melatonin, are being investigated [52]. These approaches will require rigorous evaluation of safety, biodistribution, dosing, and efficacy for future clinical translation.

3 Metabolic Reprogramming in Ageing: Warburg Effect and Melatonin's Protective Role

Ageing is associated with aberrant metabolic reprogramming reminiscent of the Warburg effect, characterised by an increase in aerobic glycolysis and a decrease in mitochondrial oxidative phosphorylation [53]. This phenomenon contributes to tissue dysfunction in conditions such as sarcopenia, type 2 diabetes and immunosenescence, perpetuating oxidative stress, chronic inflammation, and functional impairment. Melatonin emerges as a key modulator of this metabolic imbalance, reversing the Warburg-like metabolic phenotype in ageing-associated disorders [54], offering new therapeutic perspectives to preserve physiological function in advanced age.

3.1 The Warburg Effect in Sarcopenia: Mitochondrial Dysfunction and Melatonin's Metabolic Modulation

Sarcopenia, the age-related loss of muscle mass and function, is associated with a metabolic shift resembling the Warburg effect [55,56]. In aging skeletal muscle, increased reliance on aerobic glycolysis and reduced oxidative phosphorylation led to lactate accumulation and chronic energy deficits, exacerbating mitochondrial dysfunction [57]. This reprogramming is driven by upregulation of glycolytic enzymes (e.g., hexokinase, PKM2) and suppression of mitochondrial complexes, particularly Complex IV, which impair ATP synthesis and promote muscle atrophy [58]. The accumulation of dysfunctional mitochondria further amplifies oxidative stress and apoptosis, key contributors to sarcopenic pathology [59].

Melatonin counteracts sarcopenia by reversing Warburg-like metabolism [60]. In murine models, chronic melatonin administration reduces intramuscular lactate and restores Complex IV activity, enhancing mitochondrial oxidative capacity [61]. Additionally, melatonin activates SIRT1, a deacetylase that promotes mitochondrial biogenesis via PGC-1α, while suppressing PDK4, a key inhibitor of pyruvate dehydrogenase that diverts glucose toward glycolysis [57,61]. Beyond direct metabolic effects, melatonin modulates the gut-muscle axis, lowering circulating lipopolysaccharides (LPS) and reducing caspase-8-mediated apoptosis in muscle cells, thereby preserving muscle mass and strength [61].

3.2 Warburg Effect, Metabolic Dysfunction and Melatonin Regulation: A Critical Triad in Aging and Type 2 Diabetes

In type 2 diabetes, exacerbated glycolytic metabolism and mitochondrial dysfunction in peripheral tissues (muscle, liver) reflect a Warburg effect-like phenotype, characterised by an abnormal reliance on aerobic glycolysis even under conditions of adequate oxygenation [62]. This phenomenon manifests clinically in complications such as diabetic nephropathy, where transcriptomic and metabolomic studies have identified a significant increase in glycolytic intermediates (e.g., lactate) and a parallel reduction in the activity of mitochondrial complexes in the renal cortex, suggesting aberrant metabolic reprogramming [63]. In metabolic syndrome, clinical studies commonly report decreases in fasting insulin and atherogenic lipid fractions with little change in fasting glucose. This pattern is consistent with an insulin-sensitizing and lipid-modulating action rather than a direct hypoglycemic effect, and its magnitude appears sensitive to dose and nocturnal timing [64].

At the molecular level, chronic hyperglycaemia induces overexpression of PDK4 (pyruvate dehydrogenase kinase 4), a key enzyme that inhibits the PDH complex and diverts pyruvate to lactate production instead of mitochondrial oxidation. This mechanism, extensively studied in cancer (classical Warburg effect), is replicated in type 2 diabetes, perpetuating insulin resistance and oxidative stress [65]. In animal models, pharmacological inhibition of PDK4 with dichloroacetate (DCA) restores glucose oxidation and reduces lactate accumulation in diabetic kidneys, suggesting that metabolic reprogramming is reversible [66].

Melatonin emerges as a dual modulator in this context [67]. On the one hand, *in vitro* studies show that melatonin reduces apoptosis in cells exposed to high glucose levels, regulating proapoptotic proteins (Bax, caspase-3) and activating survival pathways such as Akt/mTOR [68]. On the other hand, in models of type 2 diabetes, melatonin suppresses PDK4 and reactivates PDH, facilitating pyruvate entry into the Krebs cycle and improving insulin sensitivity [29]. However, in humans, high doses of melatonin can generate paradoxical effects, such as a reduction in insulin sensitivity (HOMA-IR), highlighting the need to optimise therapeutic regimens [69].

3.3 Immunosenescence: Immunometabolic Ageing and Cellular Dysfunction

The ageing of the immune system (immunosenescence) is characterised by a metabolic shift towards glycolysis in T lymphocytes and macrophages, a phenomenon like the Warburg effect observed in tumour cells. This process is driven by the stabilisation of HIF-1α even under normoxic conditions, which reduces mitochondrial oxidative capacity and compromises the effector function of immune cells [70]. Studies in activated macrophages show that HIF-1α signalling induces the expression of glycolytic enzymes such as hexokinase and lactate dehydrogenase, diverting metabolism towards lactate production and perpetuating mitochondrial dysfunction [71]. Accumulation of lactate in the tissue microenvironment suppresses cytotoxic T cell activity and promotes chronic inflammatory responses, a hallmark of immunosenescence [70].

Melatonin counteracts these changes by key mechanisms. First, it reduces HIF-1α expression in senescent T cells, reversing glycolytic dependence and restoring oxidative phosphorylation. This effect has been observed in cancer cells, where melatonin inhibits HIF-1α stabilisation under hypoxia, reducing the expression of target genes such as Vascular endothelial growth factor (VEGF) [72]. Second, melatonin modulates mitochondrial autophagy through activation of SIRT3, enhancing the clearance of dysfunctional mitochondria and reducing ROS production in macrophages [73,74]. In preclinical models, melatonin administration in aged mice increases the proportion of naive T lymphocytes and enhances antigen responsiveness, effects associated with reduced glycolysis and increased mitochondrial complex II activity [75,76].

3.4 Clinical Evidence and Therapeutic Perspectives of Melatonin in Relation to the Warburg Effect in Aging

Melatonin has emerged as a promising metabolic modulator to address age-related disorders such as type 2 diabetes, sarcopenia and immunosenescence through its action on pathways related to the Warburg effect. In the case of type 2 diabetes, clinical studies have shown that genetic variants in the MTNR1B receptor increase the risk of this disease in humans, as melatonin inhibits insulin secretion when administered close to food intake. In carriers of these variants, melatonin administration reduces insulin sensitivity, exacerbating glucose intolerance [69]. However, in animal models, melatonin reduces oxidative stress in pancreatic β-cells and improves mitochondrial function, suggesting potential benefits in diabetic complications [77].

In the field of sarcopenia, melatonin administered in models of muscle ageing improves strength and muscle mass by reducing circulating levels of lipopolysaccharide (LPS), which promotes apoptosis via the Tnfrsf12a/caspase-8 pathway. In addition, it modulates the gut microbiota and increases beneficial metabolites such as gamma-glutamylalanine, reversing age-associated mitochondrial dysfunction [61]. These effects correlate with a significant improvement in muscle strength and a reduction in apoptosis [60].

In terms of immunosenescence, melatonin counteracts immune ageing by reducing glycolytic dependence in T lymphocytes and macrophages. In preclinical models, melatonin suppresses HIF-1α stabilisation under normoxic conditions, restoring oxidative phosphorylation and enhancing mitochondrial complex II activity. In addition, it activates SIRT3, promoting autophagy of dysfunctional mitochondria and reducing the production of ROS [17,78].

Current therapeutic perspectives underline the importance of genetic and chronobiological personalisation in the use of melatonin, recommending the avoidance of high doses and its administration close to meals in individuals at genetic risk. In addition, the combination of melatonin with physical exercise could enhance mitochondrial biogenesis and counteract aberrant metabolic reprogramming in aged tissues, although the efficacy and safety of this synergy require validation in controlled clinical studies [54,61]. Future challenges include the validation in clinical trials of the impact of melatonin on specific metabolic biomarkers of the Warburg effect, such as lactate and PDK4, as well as the development of selective MT1/MT2 receptor agonists to optimise its metabolic and circadian effects.

4 Warburg Effect and Melatonin on Metabolic Organs: Implications for Renal Pathologies

4.1 Renal Disorders: Warburg Effect and Renoprotective Role of Melatonin

The kidney, an organ with high energy demand, is particularly vulnerable to Warburg-like metabolic reprogramming in pathological contexts [63]. In diabetic nephropathy, chronic hyperglycaemia induces a shift towards aerobic glycolysis in podocytes and tubular cells, characterised by increased PDK4 (PDH inhibitor) expression and lactate accumulation in the renal parenchyma [63]. This phenomenon, validated by metabolomics studies, is associated with glomerular inflammation, oxidative stress and tubular apoptosis, processes that drive progression to renal failure [79].

Melatonin counteracts these alterations by multiple mechanisms. In models of type 2 diabetes, it reduces PDK4 expression, restoring PDH activity and facilitating pyruvate entry into the Krebs cycle [13]. In parallel, it suppresses hyperglycaemia-induced HIF-1α stabilisation, decreases transcription of glycolytic genes (GLUT1, LDHA), which could mitigate interstitial fibrosis [17]. These effects correlate with a reduction in urinary albumin excretion and a preservation of glomerular filtration rate in diabetic rats [80].

In acute kidney injury (AKI), such as ischemia-reperfusion, induces a similar metabolic phenotype, with lactate accumulation and mitochondrial dysfunction in proximal tubular cells. Progesterone-associated melatonin demonstrated a protective role against such injury by reducing oxidative stress and lactate

dehydrogenase levels [81]. In addition, it modulates autophagy by activating SIRT1, promoting the elimination of damaged mitochondria, and reducing tubular necrosis [73].

In chronic kidney disease (CKD), melatonin mitigates the metabolic stress associated with uraemia [82]. And is also effective in improving metabolic disorders associated with fatty liver [83]. Studies in animal models propose combining it with SGLT2 inhibitors, which already show synergistic metabolic effects in models of diabetic nephropathy [84]. However, clinical trials evaluating specific markers of the Warburg effect (tissue lactate, PDK4/PDH ratio) are required to validate these strategies.

4.2 Therapeutic prospects

Chronotherapeutic administration of melatonin could enhance its renoprotective action by optimising its mitochondrial activity and normalising its lactate dehydrogenase levels [85]. In parallel, studies in haemodialysis patients show that oral melatonin treatment reduces levels of oxidative stress and inflammation [86]. These effects are accompanied by an improvement in sleep quality and an expected improvement in renal fibrosis and the renin-angiotensin system [87].

The kidney emerges as another target organ where melatonin reverses aberrant metabolic reprogramming, offering new therapeutic opportunities in renal diseases. Its ability to restore mitochondrial oxidation and reduce glycolytic stress could position this molecule as a promising adjuvant in nephroprotection, although further studies are needed.

5 Cardiovascular Disorders: Warburg Effect and Cardioprotective Action of Melatonin

5.1 Heart Failure: Metabolic Reprogramming and Energy Stress

In heart failure (HF), cardiomyocytes undergo a metabolic transition to aerobic glycolysis, a phenomenon analogous to the Warburg effect [88]. Transcriptomic and metabolomic studies have identified an overexpression of GLUT1 and hexokinase-II in failing human myocytes, along with a reduction in mitochondrial complex I activity and fatty acid oxidation. This change, driven by chronic activation of adrenergic signalling and relative hypoxia, leads to an accumulation of intramyocardial lactate and an energy deficit that perpetuates contractile dysfunction [89].

Melatonin counteracts these alterations by multiple mechanisms [90]. In rat models of isoproterenol-induced HF, administration of melatonin restores mitochondrial activity while reducing lactate production, thus improving energy capacity and maintaining the expected antioxidant capacity. In addition, it reactivates the succinate dehydrogenase complex, improving the efficiency of the Krebs cycle, and increasing ATP production [91,92]. These effects correlate with a significant improvement in ventricular ejection fraction in animal models [70].

5.2 Pulmonary Arterial Hypertension: Aberrant Glycolysis and Vascular Remodelling

In pulmonary arterial hypertension (PAH), vascular smooth muscle cells and pulmonary endothelial cells adopt a cancer-like metabolic phenotype, with a very significant increase in glucose uptake and thus an over-reliance on aerobic glycolysis [93]. This phenomenon is mediated by HIF-1α stabilisation under normoxic conditions, which induces the expression of key enzymes for lactate production [94]. Lactate accumulation in the vascular microenvironment promotes vascular smooth muscle cell proliferation and the formation of plexiform lesions, pathognomonic features of pulmonary arterial hypertension [95].

Melatonin reverses this phenotype by being able to act under severe hypoxia conditions preserving the oxidative balance and being able to protect mitochondria [96] and metabolism, keeping inflammation levels low [97]. As in previous cases, however, a study directly targeting the Warburg effect and its derivations, which are clearly identified in these alterations.

5.3 Therapeutic Mechanisms and Clinical Perspectives

The beneficial effects of melatonin on cellular metabolism in heart failure have been clearly demonstrated in multiple articles [98], and the scientific community is calling for appropriate clinical trials to confirm this beneficial effect in humans [90]. Thus, melatonin has been shown to improve cardiac output, proving to be a suitable treatment and a potent palliative agent for heart failure patients [99]. Furthermore, its role as a sirtuin modulator enhances its cardioprotective capacity, particularly HF [100].

For its part, PAH, as previously described, also has ample evidence of the efficiency of melatonin and, as in the previous case, a clinical study is needed to confirm its beneficial role [101]. In PAH, it would also be interesting to carry out gender-dependent studies, as it has been shown that women develop four times more PAH than men. These differences coincide with those observed in circadian regulation [102]. This in turn is consistent with the fact that serum melatonin levels observed in a small cohort of patients were found to be decreased in patients with PAH [103]. There is certainly a strong possibility that melatonin has a role to play in the palliation of PAH [104].

6 Conclusions

The Warburg effect, originally described in the context of cancer, has been identified as a relevant metabolic phenomenon in various non-neoplastic diseases, including neurodegenerative pathologies, aging, type 2 diabetes, and renal and cardiovascular dysfunctions. This metabolic reprogramming, characterized by a preference for aerobic glycolysis and a reduction in mitochondrial oxidative phosphorylation, contributes to cellular dysfunction, oxidative stress, and pathological progression (Table 1).

Table 1: Involvement of the Warburg effect in non-neoplastic diseases

Group of pathologies	Metabolic mechanism	Main consequences
Neurodegenerative disorders (Alzheimer's, Parkinson's, Huntington's, ALS, MS, chronic cerebral hypoperfusion)	↑ PDK4 and LDH-A, stabilization of HIF-1α, diversion of pyruvate to lactate, mitochondrial dysfunction (Complex I/IV)	Neuronal energy deficit, lactate accumulation, oxidative stress, neuroinflammation, synaptic and cognitive impairment
Aging and age-related diseases (sarcopenia, type 2 diabetes, immunosenescence)	↑ Aerobic glycolysis, ↓ oxidative phosphorylation, lactate accumulation, overexpression of PDK4 and glycolytic enzymes	Muscle atrophy, insulin resistance, chronic inflammation, impaired immune function
Renal disorders (diabetic nephropathy, acute kidney injury, chronic kidney disease)	↑ PDK4 and lactate in podocytes/tubular cells, stabilization of HIF-1α, interstitial fibrosis	Tubular apoptosis, inflammation, progression to renal failure
Cardiovascular disorders (heart failure, pulmonary arterial hypertension)	↑ GLUT1/hexokinase II, ↓ fatty acid oxidation, lactate accumulation, chronic adrenergic activation and relative hypoxia	Myocardial energy deficit, pathological vascular remodeling, contractile dysfunction

Note: ALS: amyotrophic lateral sclerosis; MS: multiple sclerosis; PDK4: pyruvate dehydrogenase kinase 4; LDH-A: lactate dehydrogenase A; HIF-1α: hypoxia-inducible factor 1α; GLUT1: glucose transporter type 1.

Melatonin emerges as a multifaceted modulator that counteracts the Warburg effect by restoring mitochondrial function, inhibiting PDK4 and HIF-1α, and activating sirtuins such as SIRT3, promoting autophagy and reducing oxidative stress. In preclinical models and some clinical trials, melatonin has been shown to improve cognitive parameters in neurodegenerative diseases, reduce insulin resistance in diabetes, protect renal and cardiac function, and modulate immune response in immunosenescence (Table 2).

Table 2: Mechanisms of melatonin action on metabolic reprogramming

Principal action	Molecular pathway involved	Pathophysiological effect
Inhibition of PDK4	Reactivation of PDH complex → pyruvate entry into TCA cycle	↓ Lactate production, ↑ oxidative phosphorylation
Destabilization of HIF-1α	Suppression of glycolytic genes (GLUT1, LDH-A, PDK4)	↓ Aerobic glycolysis dependence, ↓ inflammation and fibrosis
Activation of sirtuins (SIRT1/3)	↑ Mitochondrial biogenesis (PGC-1α), ↑ mitophagy	Restoration of oxidative capacity, removal of damaged mitochondria
Direct and indirect antioxidant activity	Scavenging of ROS/RNS; ↑ SOD, GPx, CAT	↓ Oxidative stress, preservation of cellular structures
Functional protection in animal models and early clinical studies	Neuroprotection, improved muscle strength, enhanced insulin sensitivity, renal and cardiac function	Attenuation of disease progression and improvement of clinical parameters

Note: RNS: reactive nitrogen species; PDH: pyruvate dehydrogenase; TCA: tricarboxylic acid; PGC-1α: peroxisome proliferation-activated receptor γ coactivator lalpha; SOD: superoxide dismutase; GPx: glutathione peroxidase; CAT: catalase; ROS: reactive oxygen species.

Despite growing evidence, most clinical studies have not directly evaluated classic metabolic biomarkers of the Warburg effect, such as lactate or PDH activity, limiting the full understanding of its therapeutic impact. Genetic personalization and chronotherapy are emerging as promising strategies to optimize the clinical use of melatonin.

In summary, melatonin represents a promising adjuvant therapy to reverse aberrant metabolic reprogramming in multiple diseases, opening new avenues for comprehensive metabolic interventions. Robust clinical trials are needed to validate these effects and define specific administration protocols to maximize its clinical benefit.

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