Ageing Research Reviews 101 (2024) 102480

Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Review article

Dysfunctional mitochondria in age-related neurodegeneration: Utility of melatonin as an antioxidant treatment

Russel J. Reiter [a,*], Ramaswamy N. Sharma [b,**], Walter Manucha [c], Sergio Rosales-Corral [d], Luiz Gustavo de Almieda Chuffa [e], Doris Loh [f], Francesca Luchetti [g], Walter Balduini [g], Piyarat Govitrapong [h]

[a] Department of Cell Systems and Anatomy, UT Health San Antonio, Long School of Medicine, San Antonio, TX, USA
[b] Applied Biomedical Sciences, University of the Incarnate Word, School of Osteopathic Medicine, San Antonio, TX, USA
[c] Instituto de Medicina y Biologia Experimental de Cuyo (IMBECU), Consejo Nacional de Investigaciones Cientificas y Tecnologicas (CONICET), Mendoza 5500, Argentina
[d] Centro de Investigacion Biomedica de Occidente, Instituto Mexicano del Seguro Social, Guadalajara, Mexico
[e] Departamento de Biologia Estrutural e Funcional, Setor de Anatomia - Instituto de Biociências, IBB/UNESP, Campus Botucatu, Botucatu, São Paulo, Brazil
[f] Independent Researcher, Marble Falls, TX, USA
[g] Department of Biomolecular Sciences, University of Urbino Carlo Bo, Urbino, Italy
[h] Chulabhorn Graduate Institute, Chulabhorn Royal Academy, Laksi, Bangkok, Thailand

ARTICLE INFO

Keywords:
Warburg metabolism
Alzheimer disease
Parkinson disease
Huntington disease
Amyotrophic lateral sclerosis
Acetyl coenzyme A
Oxidative stress
Radical scavenging
Antioxidative enzymes

ABSTRACT

Mitochondria functionally degrade as neurons age. Degenerative changes cause inefficient oxidative phosphorylation (OXPHOS) and elevated electron leakage from the electron transport chain (ETC) promoting increased intramitochondrial generation of damaging reactive oxygen and reactive nitrogen species (ROS and RNS). The associated progressive accumulation of molecular damage causes an increasingly rapid decline in mitochondrial physiology contributing to aging. Melatonin, a multifunctional free radical scavenger and indirect antioxidant, is synthesized in the mitochondrial matrix of neurons. Melatonin reduces electron leakage from the ETC and elevates ATP production; it also detoxifies ROS/RNS and via the SIRT3/FOXO pathway it upregulates activities of superoxide dismutase 2 and glutathione peroxidase. Melatonin also influences glucose processing by neurons. In neurogenerative diseases, neurons often adopt Warburg-type metabolism which excludes pyruvate from the mitochondria causing reduced intramitochondrial acetyl coenzyme A production. Acetyl coenzyme A supports the citric acid cycle and OXPHOS. Additionally, acetyl coenzyme A is a required co-substrate for arylalkylamine-N-acetyl transferase, which rate limits melatonin synthesis; therefore, melatonin production is diminished in cells that experience Warburg-type metabolism making mitochondria more vulnerable to oxidative stress. Moreover, endogenously produced melatonin diminishes during aging, further increasing oxidative damage to mitochondrial components. More normal mitochondrial physiology is preserved in aging neurons with melatonin supplementation.

1. Introduction

Due to increasing life span, humans are outliving the optimal functional capacity of many body parts such that defective hips are replaced, dysfunctional organs are transplanted, wrinkled skin is smoothed out, etc. Advancing age and the associated faltering organs become increasingly vulnerable to diseases with organ systems undergoing an accelerated rapid downward functional spiral; thus, the older an organ is the faster it deteriorates. The rate of organ degeneration during aging is in part related to its metabolic activity with organs with high metabolic demands undergoing earlier and more insidious changes. In this context, a large number of central nervous system (CNS) neurons are estimated to

* Correspondence to: Department of Cell Systems and Anatomy, UT Health San Antonio, Long School of Medicine, 7703 Floyd Curl Dr., San Antonio, TX, USA.
** Corresponding author.
E-mail addresses: reiter@uthscsa.edu (R.J. Reiter), rsharma@uiwtx.edu (R.N. Sharma), wmanucha@fcm.uncu.edu.ar (W. Manucha), espiral17@gmail.com (S. Rosales-Corral), luiz-gustavo.chuffa@unesp.br (L.G. Almieda Chuffa), lohdoris23@gmail.com (D. Loh), Francesca.luchetti@uniurb.it (F. Luchetti), walter.balduini@uniurb.it (W. Balduini), piyarat@cgi.ac.th (P. Govitrapong).

https://doi.org/10.1016/j.arr.2024.102480
Received 21 June 2024; Received in revised form 18 August 2024; Accepted 28 August 2024
Available online 3 September 2024

be lost every day which gradually weakens an organism as it ages. Compounding the problem is that neurons are highly differentiated such that the majority of them are incapable of renewing themselves so their lost is especially devastating. As a result, neurodegenerative conditions are major factors that contribute to morbidity and mortality.

The requirement for exaggerated amounts of glucose and oxygen to support the elevated metabolic demands of neurons contributes to their decline (mitochondrial oxidative theory of aging) in part due to the byproducts of these molecules (Munro and Pamenter, 2019). In particular, spin-off products of ground state-based oxygen (O_2) cause neighboring subcellular molecules to be continually under siege and capable of being damaged which, if they are not repaired, compromise the ability of the damaged cells to flourish. These derivatives are referred to as reactive oxygen (ROS) and reactive nitrogen species (RNS), some of which are also free radicals (Sies, 2021). Free radicals, by definition, are molecules or parts of molecules that have an unpaired electron in their outermost orbital; this makes them highly reactive and often destructive to molecules in the vicinity of where they are generated, i.e., DNA, RNA, proteins and lipids; the resulting damage is referred to as oxidative or nitrosative stress. The accumulation of oxidative and nitrosative-damaged molecular components buildup throughout life gradually compromising neuronal function; this accumulation of molecular debris is recognized as a component of aging (Sies et al., 2017). The contribution of oxidative damage to age-related degeneration, known as the free radical theory of aging is a widely accepted biological premise.

Especially ROS can be generated under a variety of conditions in all subcellular compartments. For example, NADPH oxidases, aldehyde oxidases, cytochromes P450 and many others cause the formation of the superoxide anion radical ($O_2^{\bullet-}$) whereas other oxidases give rise to hydrogen peroxide (H_2O_2) (Andre-Levigne et al., 2024). In reference to their gerontological impact, however, it is the abundant ROS generated by mitochondrial electron transport chain (ETC) that is of the major interest and probably contribute most significantly to the aging phenotype (Bhattacharya et al., 2024).

Neurological aging, however, is not simply a matter of free radical damage to mitochondria. Many other molecular processes are intertwined with the changes in these organelles contributing to the aging phenotype. Some of the other related organellar dysfunctions that occur when mitochondrial physiology is disturbed are summarized in the Conclusions and Perspectives of this report. Since mitochondria have a central role in essentially every function a neuron performs, and because current data documents that melatonin is synthesized in mitochondria, this review is intended to showcase the evidence that the loss of mitochondrial and pineal melatonin in the aged may be a fundamental feature of neural degenerative diseases.

2. Relationship of melatonin to the brain throughout life

Melatonin (N-acetyl-5-methoxy tryptamine) is best known because of its circadian production and synthesis in the pineal gland, an outgrowth of the posterodorsal thalamus and a major component of the epithalamus. The mechanisms governing the production of melatonin in the pineal gland have been thoroughly described with its circadian production being determined by the light:dark environment as witnessed by the lateral eyes (Klein, 2007). In mammals, and likely in all vertebrates, pineal melatonin synthesis and secretion is normally elevated during the night. Its cyclic release aids in the regulation of the suprachiasmatic nucleus (SCN), the master circadian clock, in the basal anterior hypothalamus. Additionally, the blood melatonin rhythm directly impacts clock genes in somatic cells throughout the body. The well-regulated circadian biology of an organism is a major contributor to health maintenance (Chawla et al., 2024). With advancing age, however, pineal melatonin production wanes such that in the elderly the nighttime rise in circulating melatonin is greatly reduced compared to that which occurs in young individuals (Anghel et al., 2022). Although there is a significant variation in the degree of melatonin loss in aged humans, the nocturnal peak of blood melatonin can be attenuated by as much as 80 % in individuals beyond 60 years of age (Benot et al., 1999). Thus, the circadian influence of melatonin on biological rhythmicity in the aged is likewise diminished which leads to a marked diminution of optimal circadian regulation with an increased propensity for the elderly to develop disease.

In mammals, including the human, pineal melatonin is released in a circadian pattern not only into the blood but also into the cerebrospinal fluid (CSF) of the third ventricle (Fig. 1) (Kanematsu et al., 1989; Maurizi, 1991; Skinner and Malpaux, 1999; Tricoire et al., 2002). It is noteworthy that the amplitude of the CSF melatonin rhythm in the lateral ventricle is often much greater than that in the jugular vein blood with the nighttime levels of melatonin being much higher than those in the general circulation (Hedlund et al., 1977; Legros et al., 2014; Leston et al., 2015). CSF melatonin is transported with the movement of the cerebrospinal fluid throughout the cerebral ventricles and through the foramina that connects the fourth ventricle to the subarachnoid space which surrounds the entire central nervous system. The movement of melatonin is more rapid than originally anticipated with the circadian melatonin rhythm appearing in the human lumbar cistern CSF within roughly an hour after its release from the human pineal gland (Bruce et al., 1991). From the ventricles and subarachnoid space, respectively, melatonin readily seeps into neural tissue via diffusion and by means of specialized conduits, the Virchow Robin spaces, which surround penetrating arteries as they enter the brain and spinal cord (Fig. 1) (Reiter et al., 2014).

Legros and co-workers observed that there is an obvious gradient in the concentration of melatonin in sheep neural tissue with highest levels being in tissues nearest to the ventricle with a fall off as the distance from the ventricles increased; moreover, these levels fluctuated in line with the release of pineal melatonin into the third ventricle (Legros et al., 2014). As a result, neurons throughout the brain are exposed to the circadian CSF melatonin fluctuations every 24 hours, thus likely providing important timing information not only for the suprachiasmatic nucleus (SCN) but for other neurons and glia as well. Since the amplitude of the CSF melatonin rhythm is more exaggerated than that in the blood, it has been suggested that CSF melatonin levels are essential in impacting neural chronobiology including the regulation of the master circadian clock, the SCN (Reiter et al., 2023; Tricoire et al., 2003); by comparison, pineal-derived blood melatonin levels presumably have little impact on neural physiology. This is clearly supported by the findings of Legros and colleagues who showed that brain levels, in contrast to those from the CSF, were not impacted by blood melatonin concentrations (Legros et al., 2014). Thus, neurons and glia in the CNS may be more tightly regulated than those of somatic cells throughout the body in terms of their circadian physiology. As with blood melatonin levels, those in the CSF drop with age such that the influence on circadian rhythm regulation in the CNS is also reduced. The age-associated decline of circadian rhythm regulation throughout the body, including the CNS is readily apparent, e.g., deterioration of the sleep:wake cycle (Li et al., 2024b). The importance of well-regulated circadian rhythms for general health cannot be overstated. Distortion of these rhythms, i.e., chronic chronodisruption (Erren and Reiter, 2009) is associated with cognitive decline, neurodegenerative diseases, negative cardiovascular consequences, among others (Megha et al., 2024).

While the circadian regulation of cellular rhythms by the pineal-derived CSF and blood melatonin cycles are generally accepted as being membrane receptor-mediated (Cardinali, 2024; Xia et al., 2023), its actions at the SCN may also involve processes that are less obviously a consequence of melatonin receptor interactions (Vriend and Reiter, 2015a). The MT1 and MT2 melatonin membrane receptors are ubiquitously distributed throughout the CNS (Feng et al., 2023; Klosen, 2024) and in non-neural tissues as well (Slominski et al., 2012). Likewise, cytosolic and nuclear binding sites for melatonin may impact the action of the indoleamine at the CNS level (Bianchet et al., 2008; Venegas et al.,

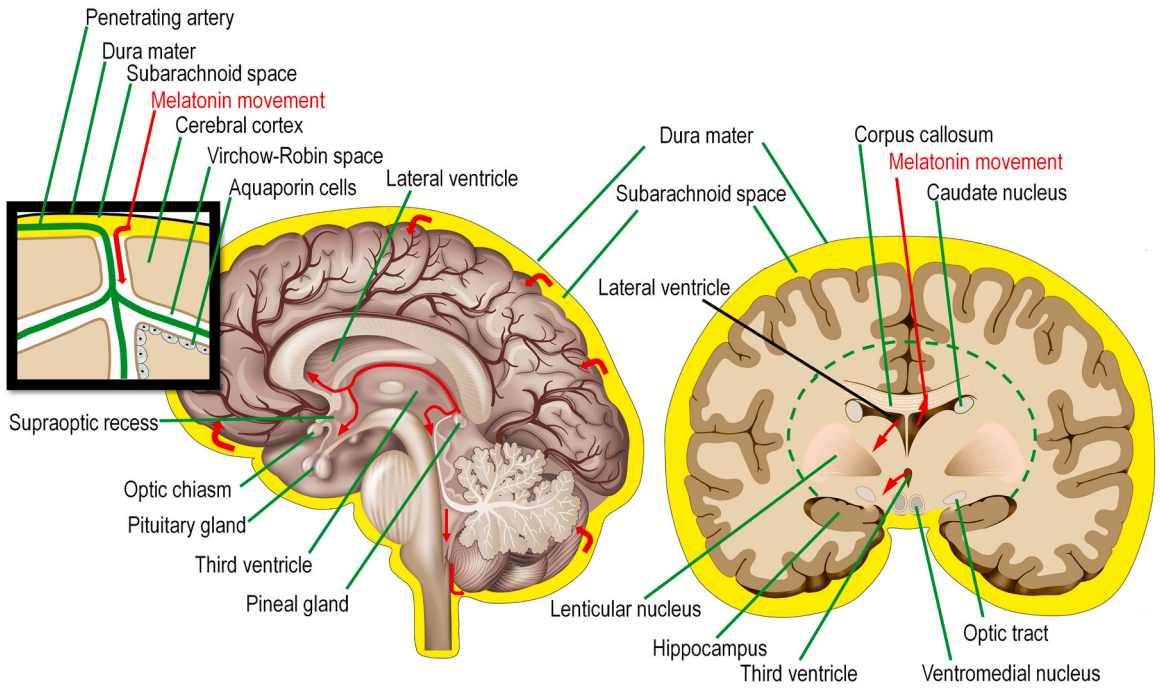

Fig. 1. Mid-sagittal (left) and frontal cross section (right) of the human brain illustrating the flow of melatonin released from the pineal gland into CSF of the third ventricle, its movement through the ventricular system, and its transport into neural tissue as described in the published literature. After its nocturnal release via the pineal recess into the posterior aspect of the third ventricle, it quickly diffuses throughout the third and lateral ventricles; the concentration in these cavities may be greater than the levels in the blood. With the movement of CSF, melatonin passes through the iter (cerebral aqueduct) to the fourth ventricle from where it enters the subarachnoid space via the foramen of Magendie and the foramina of Luschka. The subarachnoid space extends over the entire brain and spinal cord and is bound by the dura mater. From the ventricles, melatonin, presumably via simple diffusion, seeps into the surrounding tissue, the so-called white matter, with a gradient where highest levels are measured in the tissues nearest to the ventricles. The tissue is classified as white matter because of the large amount of myelin coating critical descending (e.g., corticospinal tract/pyramidal tract), crossing fibers (corpus callosum, anterior commissure, etc.) and ascending fiber tracts (e.g., medial lemniscus and continuing third order neurons, brachium conjunctivum, etc.); the ascending and descending fibers make up the internal capsule. High levels of the antioxidant melatonin in these areas are important since myelin is rich in easily oxidizable fatty acids. From the subarachnoid space on the surface of the brain, melatonin passes with CSF into the Virchow-Robin spaces (insert in left image) from where it also enters the neuropil via aquaporin 4 membrane channels. The area perfused by melatonin from the subarachnoid space of the brain is generally referred to as gray matter, because it contains large numbers of neuronal cell bodies (perikarya) such as those in the precentral motor and postcentral sensory gyri, respectively. Melatonin from the cerebral ventricles and subarachnoid space is believed to be important in influencing circadian rhythms in neural elements (neurons and glia) and in protecting these tissues from oxidative stress. The hyphenated line in the right image represents the estimated areas of white (internal) and gray matter (superficial) perfused by melatonin from the ventricles and subarachnoid space, respectively.

2013).

Pineal-derived melatonin, however, is not the only source of this indoleamine for neurons and glia, or for all other cells as well (Reiter et al., 2024). For several decades it has been assumed that many other tissues also generate melatonin; this is referred to as extrapineal melatonin production (Acuna-Castroviejo et al., 2014; Huether, 1993; Kvetnoy et al., 1997) with the list of organs that produce this molecule being expanded to potentially include every cell that contains mitochondria (Tan et al., 2013; Zhao et al., 2019), for which there are only a few exceptions. The association of melatonin with mitochondria relates to the origin of these organelles which are believed to have evolved from bacterial endosymbionts when these microbes were engulfed as nutrient energy by the earliest eukaryotes about 2.5 Mya (million years ago); this is known as the endosymbiotic theory for the origin on mitochondria and is widely accepted hypothesis by biologists (Andrieux et al., 2021). Since the ingested prokaryotes were believed to already be capable of generating melatonin (Manchester et al., 1995), this activity was preserved as they evolved into mitochondria since it was an ideal molecule, as a potent antioxidant (Hardeland, 2022), to maintain optimal mitochondrial redox homeostasis (Lei et al., 2023; Reiter et al., 2022).

Several decades ago, a report was published that provided indirect evidence that the mitochondria of pinealocytes are the intracellular site of melatonin production (Kerenyi et al., 1979). Venegas and co-workers provided more direct evidence for the production of melatonin in brain mitochondria (Venegas et al., 2012). After the fractionation of mouse cerebral cortical cells (neurons and glia), they observed differential concentrations of melatonin with greatest levels in cell membranes, followed by mitochondria, nuclei and cytosol. Mitochondria had much higher levels than those in nuclear or cytosolic fractions; the elevated levels of melatonin in membranes likely relates to its ready solubility in lipids. None of the fractions exhibited a circadian variation in melatonin concentrations (Venegas et al., 2012). The high levels in brain and liver along with the large amounts of melatonin which are reported to exist in multiple organs are not readily explained on the basis of it being solely derived from a miniscule organ such as the pineal gland. Moreover, melatonin has been identified in all invertebrates, protists and plants where tests have been performed; none of these species has a pineal gland, an organ that is unique to vertebrates.

In recent years, the possibility of mitochondria of every cell being a source of melatonin has become of extreme investigative interest and experimental evidence now supports this conclusion. Theoretically, this is consistent with the origin of mitochondria [and chloroplasts, which also produce melatonin (Zheng et al., 2017)] predictably from melatonin-synthesizing α-proteobacteria and cyanobacteria, respectively (Zhao et al., 2019). The retention of melatonin, because of its potent direct scavenging actions and indirect antioxidant functions resulting from its stimulation of antioxidant enzymes (Galano and Reiter, 2018), by these organelles throughout evolution seems to have been a fortuitous choice since mitochondria (and chloroplasts) are major contributors to free radical generation of all cells; if these reactants are

not adequately neutralized, mitochondria functionally deteriorate, and the associated cells die.

When He and colleagues incubated purified mouse oocyte mitochondria with serotonin, the forerunner of melatonin in its synthetic pathway, melatonin was generated and released it into the incubation medium (He et al., 2016). The synthesis of melatonin by the isolated mitochondria did not occur when the organelles were not supplied with supplemental serotonin. This observation is of specific importance considering the maternal contribution to all the mitochondria in a mammalian organism. Since oocyte mitochondria clearly produced melatonin, it seemed reasonable to speculate that all mitochondria that devolved from the oocyte would have retained this trait, including those of neurons and glia. Experimental evidence for the ability of specifically neuronal mitochondria to synthesize melatonin was provided a year later (Suofu et al., 2017). This group confirmed that the proteins for the two enzymes that convert serotonin to melatonin, i.e., AANAT (arylalkylamine N-acetyltansferase) and ASMT (acetylserotonin methyltransferase), are present in the matrix of non-synaptosomal mitochondria purified from mouse brain, with neither exhibiting a circadian rhythm. Additionally, when radioactive labeled serotonin was incubated with mitochondria, radioactive melatonin was generated. They also found that melatonin was released into the cytosol and found it interacted with MT1 melatonin receptors on the outer mitochondrial membrane. Finally, they performed an extensive series of studies using purified mitochondria to document the high efficacy of melatonin in reducing oxidative stress in these organelles (Suofu et al., 2017).

This group published other work that verified the essential nature of melatonin in preserving mitochondria wellbeing. Since endogenous melatonin levels are diminished in the aged which is often coincident with neurodegenerative changes and neural inflammation, they anticipated that the reduction in melatonin underpinned these conditions (Jauhari et al., 2020). Using an AANAT knockout model, they found that the reduction in mitochondrial melatonin caused activation of neuronal DNA-mediated inflammation, a disorder characteristic of neural degeneration in the elderly. Because of their specific interest in Huntington's disease (HD), Kim and colleagues (Kim et al., 2023) investigated melatonin biosynthetic capacity of the pineal and brain regions collected from individuals who died of this condition. AANAT expression was depressed in both the pineal and striatum of HD patients. The conclusion was that melatonin synthesis is disrupted in the pineal and brain of HD patients, an experimental condition in which melatonin treatment improves outcome.

The *de novo* synthesis of melatonin has also been documented in the choroid plexus which, if released, would contribute to the high levels of melatonin in the CSF (Quintela et al., 2018). Using rat choroid plexus, this group showed that the enzymes required for the conversion of serotonin to melatonin, i.e., AANAT and ASMT, are localized specifically in the mitochondria of these secretory cells. They also used pig choroid plexus explants to further document the *de novo* melatonin production in this tissue. Whether melatonin synthesis in the choroid plexus exhibits a circadian rhythm was inconclusive and there was no definitive proof that this tissue actually released melatonin into the CSF; however, the localization of AANAT was unambiguously associated with the mitochondria.

Herein, we stress that the high levels of melatonin in the mitochondria are primarily due to its *de novo* synthesis in these organelles which is supported by the presence of the melatonin-forming enzymes. Pineal-derived, blood-transported melatonin, however, could also diffuse into these organelles via specific channels, e.g., PEPT1/2 transporters (Huo et al., 2017). As already mentioned, however, considering the small volume of pineal tissue, this exclusive source alone would simply be inadequate to account for the high levels of melatonin in the multi-trillion mitochondria present in an organism.

Some of most interesting data regarding extrapineal melatonin production has been observed in situations where the stimulation of the innate immune response in peripheral organs activated local melatonin production while inhibiting its synthesis in the pineal gland (Markus et al., 2021). The local induction of melatonin synthesis in the CNS at the expense of its production in the pineal gland also occurs in the cerebellum during an acute neuroinflammatory response following the injection of lipopolysaccharide (LPS) into the CSF of rats (Pinato et al., 2015). This treatment led to a reduction in the nocturnal peak of pineal-derived plasma melatonin with a concurrent rise of its synthesis in the cerebellum although not in the cerebral cortex or hippocampus. Stimulation of cerebellar melatonin production was associated with an increased nuclear factor kappa B (NF-κB) which induced the activity of the rate liming enzyme in melatonin synthesis, AANAT. The locally generated melatonin prevented the neural toxicity of LPS in the cerebellum, but the protection did not extend to the cortex or hippocampus where *de novo* melatonin synthesis did not occur. The bidirectional interaction between the biosynthetic machinery for melatonin production in the pineal gland and peripheral tissues requires more thorough investigation since they may have important functional implications for the control of discrete pockets of inflammation throughout the body. Additionally, these findings prove that extrapineal melatonin synthesis is inducible in mammals, a response which is very well documented in plants (Ahammed et al., 2024); in this case it occurred during an inflammatory response where free radicals are generated in excess. This has important implications since the additional melatonin would resist the tissue damage associated with toxin exposure, and possibly other free radical-inducing processes if it is inducible as a result of other stimuli via a feedforward process, which we consider a possibility (Tan et al., 2015).

In a recently published report, Xing and co-workers mono-colonized the gut of germ-free mice with a mutant strain of *E.coli* that was incapable of producing indoles and compared them to a group of mice mono-colonized with indole producing *E.coli* (Xing et al., 2024). The mice lacking indole producing gut microbes exhibited numerous functional deficiencies in multiple organs including inhibition of antioxidant enzymes and elevated oxidative stress. Associated with these changes was a marked rise in serum melatonin levels which the authors felt was a compensatory response to the reduction in GPx activity which would result in an accumulation of oxidative damage. This evidence supports the conclusion that in animals, as in plants (Gu et al., 2021) melatonin production is inducible, perhaps as a result of increased free radical generation. The authors surmised that the melatonin in the serum was derived from the gut (Xing et al., 2024); if that interpretation is valid, it also means that under some dysfunctional metabolic conditions, extrapineal melatonin can be released into the blood, a process that does normally not occur from extrapineal tissues.

Considering the extensive published literature related to melatonin supplementation in deferring aging related changes in multiple organs including the CNS, it is important that these associations be more thoroughly investigated. This would be essential to not only improve longevity but, more importantly, to prolong the health span of older individuals. Melatonin, as an endogenously produced molecule can be supplemented for long durations without untoward side effects (Garcia et al., 2020; Martin Gimenez et al., 2022).

3. Neural mitochondria under siege

With justification, mitochondria are attracting increasing investigative attention as a multifunctional subcellular organelle. While their role in energy production has long been known, in the last 3 decades virtually every function carried out by the cell has been shown to require participation of the mitochondria. Beyond their well-known role in ATP generation which requires oxygen consumption with the production of carbon dioxide and the shunting of electrons between the complexes of the electron transport chain (ETC), mitochondria stimulate the development of the transmembrane potential due to the movement of hydrogen ions between the matrix and intermembrane space (Azbarova and Knorre, 2023), they synthesize steroids (Bartman et al., 2024) and

long chain fatty acids (Lee et al., 2024a), and are involved in calcium buffering (Novorolsky et al., 2023), etc.

The ETC consists of proteins (Complexes I through IV) that function as one electron shuttles located in the inner mitochondrial membrane that culminate in the production of energy (ATP) (Fig. 2) (Lygate, 2024). The available evidence indicates that Complex I and Complex III (a ubiquinol-cytochrome reductase), which leak electrons, reduce nearby O_2 to the $O_2^{\bullet-}$. Complex I produces $O_2^{\bullet-}$ which are directed toward the mitochondrial matrix while from Complex III they enter both the matrix and intermembrane space (Jezek et al., 2024). It is estimated that under stable conditions only a small percentage (<3 %) of electrons that are moved through the ETC are diverted to form $O_2^{\bullet-}$; however, this percentage can be greatly increased when proteins of the ETC are damaged by toxins, respiratory chain inhibitors, inflammation, elevated respiratory activity, etc. These observations support the association between metabolic rate, i.e., O_2 utilization, and the life span of cells as well as of individuals.

A characteristic of ROS and free radicals, in most cases, is their ultrashort half-lives. This is especially the case with the most destructive of the radicals, namely ·OH, which is generally believed to account for well

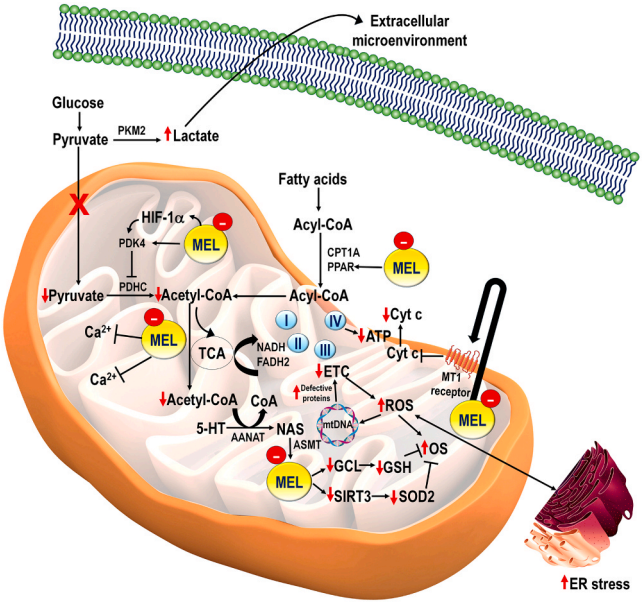

Fig. 2. This figure illustrates the consequences of pathological neurons switching from conventional mitochondrial OXPHOS to cytosolic glycolysis for the production of ATP; this metabolic change characterizes Warburg-type metabolism. Warburg-type metabolism occurs when pyruvate does not enter the mitochondria (red X); this limits the synthesis of acetyl CoA, which is vital in feeding the tricarboxylic cycle (TCA) and supporting OXPHOS. Acetyl CoA is also an essential substrate which functions in concert with serotonin (5HT) for the synthesis of N-acetylserotonin (NAS). Since acetyl CoA is diminished during Warburg-type metabolism, so is NAS; as a result, the amount of melatonin (-MEL) is likewise reduced in mitochondria. The diminished level of melatonin, a multifunctional antioxidant, allows the generated reactive oxygen species (ROS) to damage an increasing number of molecules, referred to as oxidative stress (OS). Additionally, melatonin, via stimulation of SIRT3, normally upregulates the antioxidant enzyme superoxide dismutase 2 (SOD2), allowing for inhibition of additional OS. Finally, melatonin enhances glutathione (GSH), an important mitochondrial antioxidant, by stimulating its rate limiting enzyme glutamine cysteine ligase (GCL); this action is also lower with the deficiency of melatonin adding to the OS burden. During Warburg-type metabolism, the electron transport chain (ETC), especially at Complexes I and III, leak additional electrons resulting in an augmented production of ROS. Moreover, ATP levels are reduced. Mitochondrial melatonin can escape to the cytosol from where it feeds back onto the MT1 melatonin receptor to limit the release of cytochrome c; as a consequence, cellular apoptosis is decreased. AANAT = arylalkylamine N-acetyltransferase; ASMT – acetylserotonin methyltransferase.

over 50 % of the damage these species collectively inflict (Halliwell et al., 2021). Thus, when formed, the ·OH must be immediately neutralized or it damages a nearby molecule; since the oxidize molecule is in the immediate vicinity of where the ·OH was formed, it is referred to as being on-site (Richards et al., 2015). Since free radicals are abundantly generated in multifunctional mitochondria, having an efficient radical scavenger in sufficient concentrations in place to neutralize these damaging molecular brigands would certainly be a benefit, especially if it was also inducible. Preliminary data supports the possibility that melatonin meets these important criteria.

Cells vary widely in terms of the number of mitochondria they contain. Their density in a particular cell relates to the energy demands of that specific cell. ATP-needy cells, such as neurons and cardiomyocytes, have a higher concentration of mitochondria than do most other cells. Accordingly, if not well protected these cells deteriorate more rapidly than those in other organs, correlating with the number of age-related diseases that these organs manifest (Csiszar et al., 2024; Singh et al., 2024). Moreover, as these highly- metabolically active cells decline in function, the situation worsens possibly related to the increased generation of ROS/RNS resulting from low grade chronic inflammation ("inflammaging") and changes in the activities of oxidases. Elevated free radical production in cells is characteristic of aging (Shabalina et al., 2024). The molecular damage would be further magnified if it is associated with a diminished endogenous melatonin production in senescent tissues, which is believed to be the case; moreover, the drop in melatonin is associated with a reduction in the total antioxidant capacity as measured in the blood of aged humans (Benot et al., 1999). At this point, the published findings are consistent with this scenario, but more supporting data is required to solidify these concepts. Aging is a complex process which involves the participation of many different cell types and molecular events, many of which involve mitochondrial dysfunction (Lee et al., 2024b)

As long as mitochondria are producing ATP, they are under continual bombardment by partially reduced oxygen species which have the capability of damaging proteins, lipids, DNA, etc. Considering their essential role in energy formation as well as many other functions central to cell survival, it is imperative that these organelles be equipped with the defenses necessary to maintain them in a healthy state for as long as possible. We feel that the melatonin synthesized in the mitochondrial matrix is an important component of that defensive posture.

4. Melatonin: A firewall protecting mitochondria from ROS/RNS

Melatonin is ubiquitously functional in terms of its ability to reduce oxidative/nitrosative stress. This has been documented in thousands of publications under circumstances where the molecular damage was induced by an extensive array of toxins (e.g., paraquat, ochratoxin, etc.), medications (ibuprofen, aspirin, prescription medications, etc.) or disease models (ischemia/reperfusion, Alzheimer's disease models, etc.) (Hardeland, 2019; Joseph et al., 2024; Reiter et al., 2008). Also, these beneficial actions have been confirmed in every cell and every species where it has been challenged to do so, e.g., in vertebrates, invertebrates, protists and plants (Anisimov, 2003; Gu et al., 2021). Melatonin's ability to directly neutralize highly unstable ROS has been confirmed using many available techniques, including electron spin resonance spectroscopy (Bromme et al., 2002; Tan et al., 1993), considered the gold standard for radical detoxification verification (Maffeis et al., 2024; Orlinska et al., 2024). That melatonin particularly functions in mitochondria as an antioxidant has been verified in numerous experimental models and situations (Gu et al., 2024; Jou et al., 2019; Suofu et al., 2017).

Of major importance relative to the ability of melatonin to function in the reduction of oxidative stress relates to what is referred to as the antioxidant cascade (Tan et al., 2003). One product that has been of special interest is this regard is AMFK (N-acetyl-N-formyl-5-methoxykynuramine) which is formed as a by-product of melatonin when it

scavenges ROS or when melatonin is enzymatically cleaved resulting in the formation of this kynuramine (Tan et al., 2015). Like melatonin, AFMK is a potent radical scavenger (Hardeland et al., 2009; Ressmeyer et al., 2003). A host of other melatonin metabolites contribute to the reduction of oxidative stress by quenching free radicals (Alvarez-Diduk et al., 2015; Perez-Gonzalez et al., 2017; Tan et al., 2014) (Fig. 3); in some cases, the metabolites are actually more efficient scavengers that melatonin itself (Galano and Reiter, 2018). Since some of these products are sequentially formed when neutralizing radicals, this is referred to as the antioxidant cascade and allows melatonin and its metabolic kin to scavenge multiple ROS (Tan et al., 2003). While the amount of information on this subject is meager, melatonin reportedly is also capable of repairing oxidized DNA (Perez-Gonzalez et al., 2019).

Melatonin has other actions which allow it to serve as a redox buffer at the mitochondrial level. Melatonin has long been known to be a stimulus for the glutathione peroxidase/glutathione reductase network, which exists in the mitochondrial matrix (Sies and Jones, 2020). While melatonin also stimulates the antioxidant enzyme, catalase, it is not located in the mitochondria of most cells. The literature relative to an action of melatonin on the peroxiredoxin antioxidants is rather incomplete and while melatonin promotes the activities of these enzymes under certain circumstances, whether this occurs in mitochondria has not been clarified (Hasan et al., 2018; Rossi et al., 2023).

The most destructive of the free radicals generated, ·OH, is not enzymatically degraded and the damage it inflicts can only be minimized if it is immediately scavenged after its generation. A variety of radical scavengers are readily capable of neutralizing this highly toxic agent, but only when they are in the immediate vicinity of where it is produced since it damages an adjacent molecule essentially instantaneously upon its formation. ·OH is formed via the Fenton/Haber Weiss reaction which requires the participation of a transition melatonin, most often Fe^{2+}. This rection takes place in both the cytosol and in the mitochondrial matrix (Jomova et al., 2024). Molecules that chelate heavy metal ions and make them unavailable for the Fenton reaction are an important means for limiting the transformation of H_2O_2 to the ·OH. Limson and colleagues originally described the ability of melatonin to chelate a variety of heavy metals (Limson et al., 1998). Subsequently, this action was verified by a number of workers. Galano and colleagues extended the findings to show that the metabolites of melatonin, C3OHM (cyclic 3-hydroxymelaotnin), AFMK and AMK (N-acetyl-5-methoxykynuramine) share this important property (Galano et al., 2015). In addition to being produced in mitochondria, when administered exogenously, melatonin is taken up by these organelles (Acuña-Castroviejo et al., 2018; Huo et al., 2017) so it is available for both scavenging and metal chelation.

A major means by which melatonin may control the redox state of

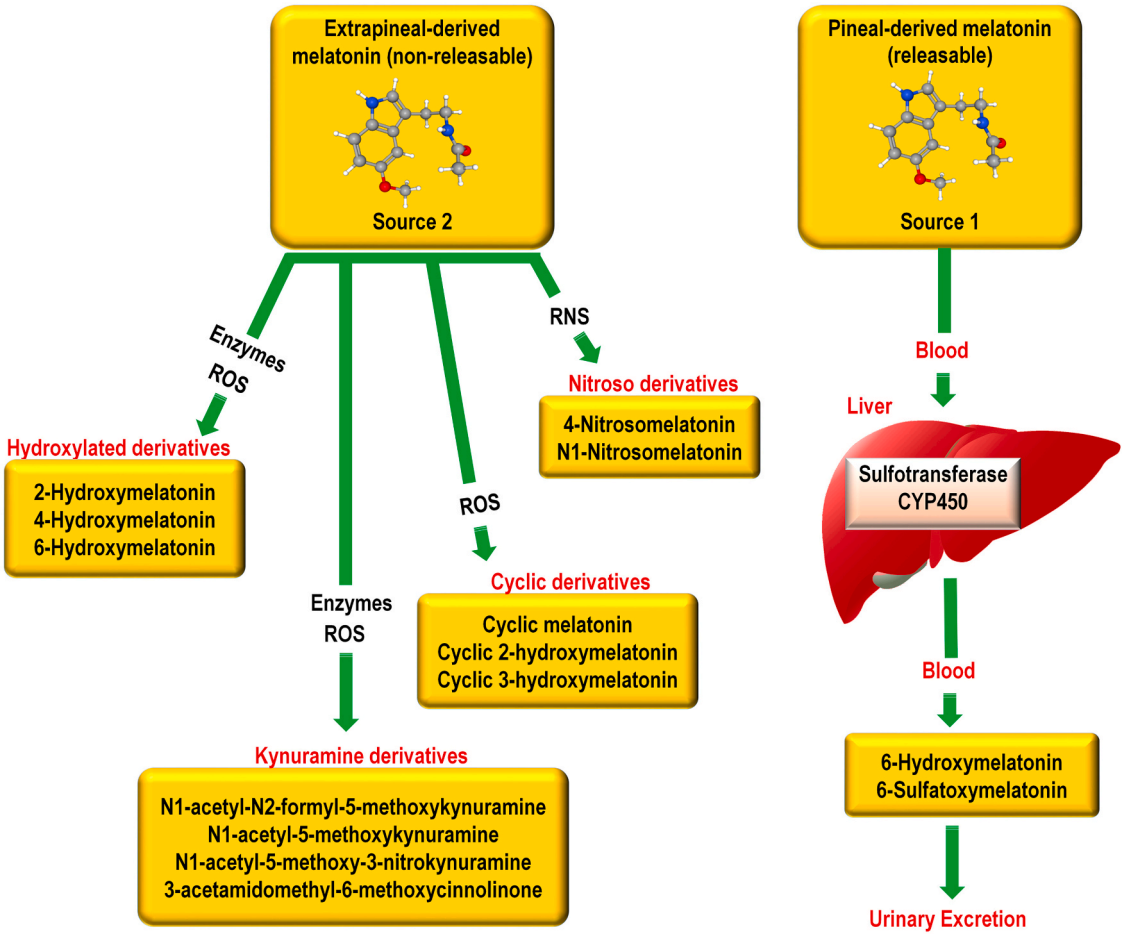

Fig. 3. This illustration identifies the two sources of melatonin, i.e., extrapineal-derived from the mitochondria (of most cells) and pineal-derived melatonin. The diagram on the left also lists the metabolites that are formed when melatonin either scavenges reactive oxygen species (ROS) or reactive nitrogen species (RNS); in some cases, melatonin is also metabolized to its derivatives by enzymes. Like melatonin itself, the metabolic kin that are produced are equally as effective or better than melatonin in directly detoxifying highly reactive species. Extrapineal-derived melatonin is not generally released from the cell in which it is synthesized. i.e., it works locally to maintain redox homeostasis in its cell of origin or possibly in immediate adjacent cells. In the right diagram, the secretion, its hepatic metabolism and the urinary excretion of the metabolites of conventionally pineal-derived melatonin is summarized. Pineal-derived melatonin is also released into the CSF and permeates into the brain where its fate is as in the left diagram. Enzymes involved in the breakdown of melatonin include cytochrome P450, myeloperoxidase, melatonin 2-hydroxylase, horseradish peroxidase, indoleamine 2,3-dioxygenase, and eosinophil peroxidase.

mitochondria is via its regulation of glucose processing in cells. In normal healthy cells (except embryonic cells early in development) in adult tissues, the end product of glucose metabolism in the cytosol, pyruvate, is transported into mitochondria where it is metabolized to acetyl coenzyme A (acetyl CoA) by pyruvate dehydrogenase complex (PDC; a combination of three enzymes) (Burns and Manda, 2017). Acetyl CoA has multiple essential functions in the mitochondria such as feeding into the citric acid cycle (He et al., 2023; Wang et al., 2023). Additionally, however, acetyl CoA is also required for mitochondrial melatonin synthesis by serving as a co-substrate/co-factor for the conversion of serotonin to the precursor of melatonin, N-acetylserotonin (Fig. 3) (Reiter et al., 2020; 2021a). As a result, a reduction in mitochondrial acetyl CoA may become rate-limiting in mitochondrial melatonin synthesis. This would lead to a drop in intramitochondrial melatonin levels and considering the diverse antioxidant functions of it and its metabolites, a reduction in melatonin concentration in this organelle may exaggerate the level of oxidative stress, modify ATP synthesis, change cellular fate due to the increased likelihood of apoptosis, alter mitochondrial dynamics, etc. (Klimova et al., 2019; Moiseenok and Kanunnikova, 2023; Zimmermann et al., 2024).

Mitochondrial acetyl CoA production is altered as a result of a change in cellular glucose processing referred to as Warburg type metabolism. Warburg type metabolism is associated with many types of cancers but also occurs in other serious pathologies (Fig. 3) (Reiter et al., 2021b); it happens when the product of glucose processing in the cytosol, pyruvate, does not enter the mitochondria to generate acetyl CoA due to the inhibition of PDC by pyruvate dehydrogenase kinase (PDK) (Barba et al., 2024). As an alternative, pyruvate is acted upon by lactate dehydrogenase and is converted to lactate; this molecule is discharged from the cell via the monocarboxylate transporter and acidifies the cellular microenvironment, which generally worsens the specific pathology (Dai et al., 2024). The decreased level of acetyl CoA in mitochondria serves as a bottle neck for melatonin synthesis and its levels in cancer cells are half those in normal tissues (Cucielo et al., 2023; Gaiotte et al., 2022; Reiter et al., 2019). The low acetyl CoA-mediated reduction in the antioxidant melatonin puts the mitochondria and cells in jeopardy of increased oxidative damage since more free radicals go undetoxified and have the opportunity to destroy adjacent healthy molecules (Fig. 3). Treating Warburg-type metabolizing cells with exogenous melatonin inhibits this process and converts cells back to the normal glucose processing and oxidative phosphorylation thereby presumably restoring mitochondrial acetyl CoA levels and elevating intramitochondrial melatonin production (Mao et al., 2016).). In human patients as well, melatonin reversed Warburg type metabolism in subjects suffering with non-small cell cancer (NSCC) and increased the efficacy of drugs used to treat this condition (Chen et al., 2021).

Pathological neurons often exhibit Warburg type metabolism and redirect pyruvate into the mitochondria restores mitochondrial redox homeostasis; examples of diseases where this aberrant metabolism occurs include Alzheimer's, Parkinsonism, amyotrophic lateral sclerosis and others (Reiter et al., 2021b). The ability of melatonin to interfere with Warburg type metabolism presumably relates to its inhibitory action of hypoxia inducible factor 1α (HIF1α), which suppresses the activity of pyruvate dehydrogenase kinase (PDK) which disinhibits PDC allowing pyruvate to enter the mitochondria followed by its conversion to acetyl CoA such that the limited availability of acetyl CoA no longer is a factor in the amount of melatonin synthesized in the mitochondria (Fig. 3) (Mota et al., 2019). These actions of melatonin are reminiscent of those using dichloroacetate, a pharmacological agent that also reverses Warburg type metabolism, perhaps by the same signaling pathway as melatonin and has generated interest as a useful pharmaceutical drug to treat several diseases (Chen et al., 2024b; Kakafika et al., 2024). It has limitations regarding its side effects, actions that do not accompany melatonin use (Bianchi et al., 2024).

That perturbed glucose processing and altered mitochondrial metabolism as a negative feature of age-related neuronal degeneration have become a subject of major interest to neurobiologists (Grimm and Eckert, 2017). In hippocampal neurons, the incidence and degree of Warburg-type metabolism (glycolysis) is enhanced during aging in mice which leads to synaptic loss and cognitive decline (Zhou et al., 2024), Genetic manipulations which reversed the heightened rate of glycolysis also reduced neuronal destruction. Based on their findings, the authors point out that manipulating glucose processing in aging neurons may be a means of deferring age-related biobehavioral decline. This approach may also be applicable to other diseases where Warburg type metabolism is a characteristic of cellular pathology. Given that melatonin reconfigures glucose processing such that mitochondrial OXPHOS is featured, its supplementation during aging may be a means of slowing the progression of these diseases (Reiter et al., 2021b)

5. Mitochondrial biomolecular condensates and free radical-mediated neural aging

The increase in mitochondrial dysfunction in neurons and in other cells perpetuates a vicious cycle that promotes the formation of aberrant protein aggregates associated with a myriad of age-related diseases (Bartman et al., 2024), actions known to be suppressed by melatonin. Age-dependent neuronal dehydration and inability to neutralize excess free radicals contribute to elevated mitochondrial matrix viscosity and molecular crowding. The resultant gain in entropy favors the formation of membraneless biomolecular condensates (BCs) via liquid-liquid phase separation (LLPS) (Park et al., 2020). LLPS is a thermodynamic process used by all tested organisms to rapidly assemble/disassemble BCs. These dynamic, micron-scale compartments organize cellular biochemistry by increasing/decreasing/excluding/sequestering reactants/enzymes/substrates to accelerate/slow/inhibit/promote cellular reactions and functions. When BCs are not disassembled in a timely manner, the aging of BCs often leads to the formation of amyloid fibrils on condensate surfaces (Linsenmeier et al., 2023). The spontaneous generation of ·OH and H_2O_2 at the electrochemically active interface of condensates further stimulates amyloid β aggregation by free radical polymerization (Majid and Garg, 2024). Both the ·OH and H_2O_2 are normally detoxified by melatonin.

The maintenance of mitochondrial dynamics/bioenergetics and OXPHOS competence is highly dependent upon the effective assembly/disassembly of BCs in mitochondria. The Mieap protein undergoes LLPS, forming BCs that selectively concentrate either enzymes or substrates to promote the biosynthesis and remodeling of cardiolipin (Ikari et al., 2024). Cardiolipin, which is protected from oxidation by melatonin, is an essential mitochondrial phospholipid that maintains cristae structure and docking of OXPHOS enzymes/super complexes. Cardiolipin composition and structure is, therefore, correlated with mitochondrial bioenergetics and ATP production, and the dysregulation of Mieap LLPS results in mitochondrial dysfunction. FUS and TDP-43 are RNA-binding proteins that undergo LLPS, forming pathological protein aggregates associated with neurodegenerative diseases (Carey and Guo, 2022). Both FUS and TDP-43 accumulate in the cytosol and in mitochondria, where FUS inhibits ATP production by suppressing the formation and activity of ATP synthase complexes, resulting in the loss of mitochondrial cristae, and fragmentation of mitochondria. Similarly, the accumulation of TDP-43 in neuronal mitochondria causes significant mitochondrial impairment via increased production of ROS, loss of cristae, and suppression of ATP production (Wang et al., 2019). Notwithstanding, LLPS also modulates the activation of transcription factors and chaperones to maintain proteostasis thereby preventing the aggregation of misfolded proteins in mitochondria (Zhang et al., 2022).

Mitochondrial chaperones and small heat shock proteins can co-phase separate and incorporate into BCs, preventing aggregation of amyloid fibrils and promoting the disassembly of pathological aggregates including FUS and TDP-43. While the dependence of chaperones on ATP is well-known, the role of ATP as a quintessential co-solute that can modulate LLPS of BCs in a biphasic manner is being investigated

with growing interest (Hautke and Ebbinghaus, 2023). The unique combination of the highly charged triphosphate group with the hydrophobic, aromatic adenosine moiety not only confers thermodynamic stability in BCs, but also amplifies the solvation effect of the hydrophilic triphosphate group, inducing protein folding and suppressing pathological aggregation (Kuramochi et al., 2024). Melatonin significantly enhances the adenosine moiety effect via π-π stacking of the indole ring and adenine (Hautke and Ebbinghaus, 2023). Specifically, melatonin augments the solubilizing effect of ATP by binding water molecules at five specific sites (Rodrigues et al., 2021), while its ability to scavenge ·OH and H_2O_2 at BC interfaces further inhibits the formation of amyloid aggregates (Loh and Reiter, 2024, 2021).

6. Neuronal mitochondrial metabolic dysfunction: reversal with melatonin

Mitochondria are ubiquitously functional subcellular organelles that are involved in virtually every aspect of cell physiology from energy production, redox signaling and homeostasis and to life and death decisions of the cell. The importance of this is further magnified in neuronal mitochondria which have very high requirements for both glucose and oxygen (Singrang et al., 2024). As a result, their precise physiological regulation is required in the maintenance of neuronal and mitochondrial quality control throughout life. Reductions in the protective mechanisms of neuronal mitochondria do not go unnoticed in terms of dysfunction and deterioration. Within the last three decades, melatonin has been at the center on many investigations that examined its efficacy in protecting the CNS from ischemia/reperfusion injury (Tozihi et al., 2023; Zhang et al., 2024a), inflammation (Pourhanifeh et al., 2024; Tauber and Nau, 2023), neurodegenerative diseases of the aged (Talbot et al., 2023; Zhang et al., 2024b), etc. Each of these serious conditions is accompanied by mitochondrial failure with the reported benefits of melatonin being related to its ability to improve mitochondrial welfare because it resists molecular damage due to excessive free radical production (Lei et al., 2023).

Melatonin has been widely tested as a treatment for a large variety of neurodegenerative pathologies where mitochondrial dysfunction has a major aspect on the disease (Giri et al., 2024; Talbot et al., 2023). The

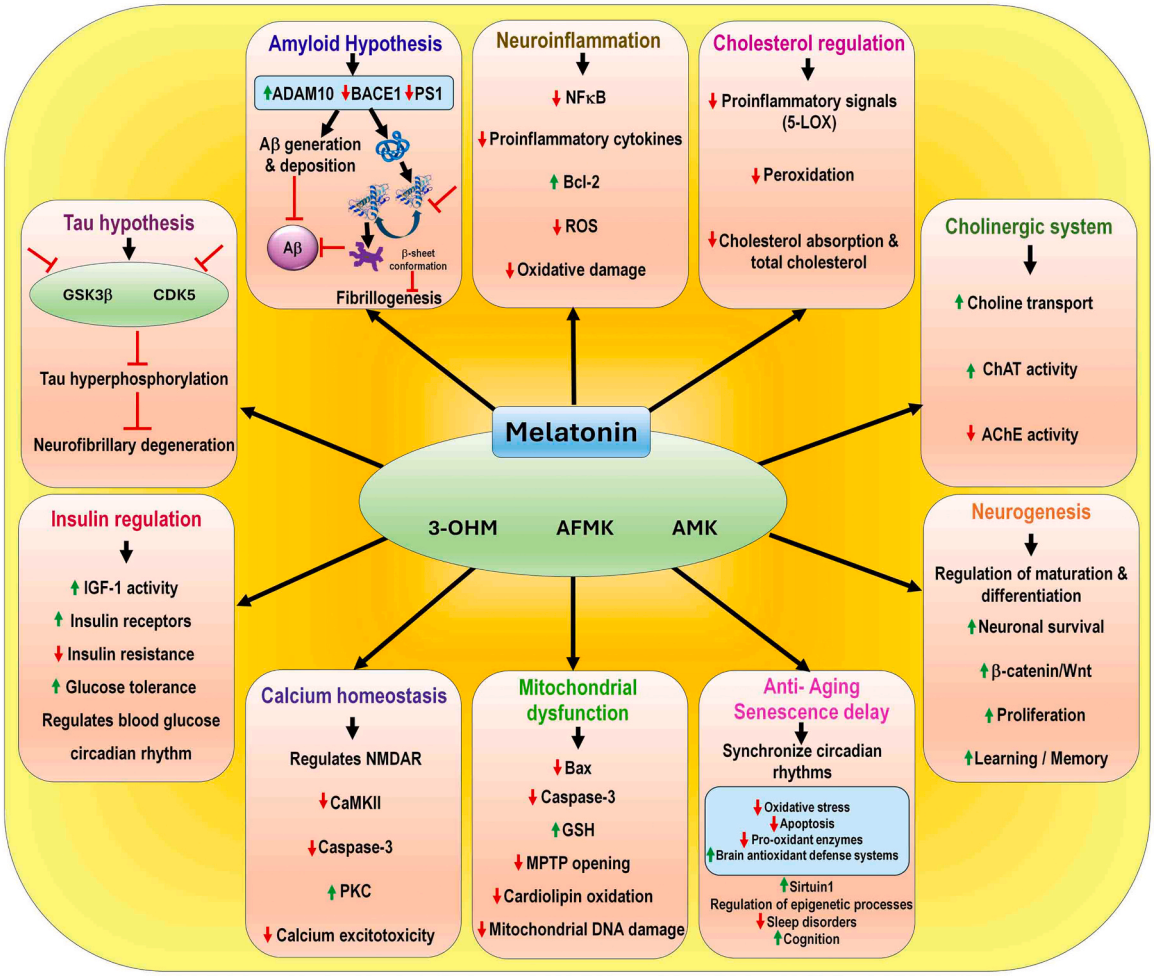

Fig. 4. As illustrated in the figure, which uses Alzheimer's disease as an example, there are often many factors that contribute to a specific neurodegenerative condition. Illustrated here are the multiple theories explaining the basis for the development of age-related, devastatingly demeaning Alzheimer's disease. Moreover, the figure identifies the actions of melatonin and its metabolites in inhibiting the progression of this disease by showing their actions on each of the theories that have been proposed to explain this condition. The ambiguity in understanding the basis of Alzheimer's disease and also other age-related neurodegenerative conditions is emphasized by the number of theories that have attempted to identify their root cause. Moreover, although the morphopathological features of a disease are often ascribed to a specific condition, there is significant degree of overlap of not only the neuroanatomical changes but of the overt pathophysiological expression of the individual diseases. Without a better understanding of the molecular mechanisms involved, it is difficult to design drugs to combat the condition. As illustrated here, melatonin works at multiple sites to potentially forestall the onset or progress on this neurodegenerative condition. These actions combined with its high safety profile and given that is inexpensive, it should be given consideration as a treatment for age-related neurodegenerations generally. Figure adapted with permission (Shukla et al., 2017).

most common neurodegenerative disorder affecting humans is Alzheimer's disease (AD). A major morphological characteristic of this debilitating cognitive condition is excessive amyloidogenesis in the CNS with the buildup of amyloid plaques (amyloid β protein) which initially appear in the hippocampal region and gradually develop in other areas of the brain as well (Nopparat et al., 2022; Picard et al., 2010; Rosales-Corral et al., 2012b). A second major feature of AD is the formation of intraneuronal tangles of the phosphorylated protein, tau. This microtubule-associated protein normally physiologically maintains microtubule stability but when phosphorylated, it becomes a major pathogenic feature of AD and other tauopathies (Akbar et al., 2016). AD presents with a variety of dementia symptoms that lead to diminished cognition, memory loss, linguistic distortions and reduced self-care. Satisfactory pharmaceutical treatments for AD are limited and typically are directed toward minimizing the symptoms and potentially retarding the progression of the disease.

The involvement of neuronal mitochondrial dysfunction in AD is well documented; this disturbance is presumably related to the accumulation of toxic Aβ, a product of amyloid precursor protein breakdown which impacts the mitochondria (Fig. 4) (Devi et al., 2006; Wang et al., 2020). Even more so than for some other cells, neurons rely heavily on oxygen and glucose to support the high levels of energy required for optimal function and, thus, any perturbation in mitochondrial physiology has a major impact on neuronal function. The mitochondria of AD cells often undergo repeated fission at the expense of mitochondrial fusion thereby leading to energy deficits. Concurrently, the redox environment of the mitochondria favors excessive ROS generation (Lee and Yoon, 2016). This contributes to damage to the proteins of the ETC and reduces ATP production and gene expression. Metabolically, the cells reprogram glucose processing and acquire a Warburg type metabolism which precludes the conversion of pyruvate to acetyl CoA in the mitochondria thereby decreasing acetyl CoA levels which normally support the tricarboxylic acid cycle and OXPHOS. Warburg type metabolism with depressed mitochondrial OXPHOS is a feature of many pathological cells and its prevention or reversal has been considered as a target to treat these diseases (Lei et al., 2023; Reiter et al., 2021b). Associated with the metabolic disturbances, calcium transfer between the mitochondria and ER also becomes imbalanced with this disruption contributing to inadequate ER-mitochondrial communication and increasing the vulnerability of the neuron to apoptosis (Kumar and Maity, 2021).

In a mouse model of AD, melatonin reversed the abnormal expression of proteins involved in mitochondrial energy metabolism and mitigated mitophagy, thereby reducing Aβ levels while improving cognitive functions (Chen et al., 2021). At the mitochondrial level in AD cells, melatonin is crucial for reducing mitophagy vesicles and mitophagy-related factors (Parkin, PINK1, LC3-II/LC3-I), as well as amyloidogenic amyloid precursor proteins (BACE1, APP, and CTFβ) (Sun et al., 2020). Mitochondria isolated from brain regions such as the cortex, hippocampus, and striatum of AD models treated with melatonin showed restored mitochondrial respiratory function, membrane potential, and ATP levels (Dragicevic et al., 2011)

Without question, different Aβ species interact with mitochondria in the AD brain. Aβ can accumulate in these organelles leading to mitochondrial structural damage, reduced metabolic function, and increased oxidative stress. These changes compromise the ability of mitochondria to produce energy and perform their vital cellular functions, which contribute to neuronal damage and the progression of AD (Rosales-Corral et al., 2012a). Understanding the relationship between Aβ and mitochondrial dysfunction is a relevant area of research for potential therapeutic interventions in this devastating neurodegenerative condition. Considering melatonin's beneficial actions at the mitochondrial level in many cell models, it is likely to have similar favorable actions in AD neurons. The multiple potential actions of melatonin in impacting the onset or progression of AD are summarized in Fig. 4.

Parkinson's disease (PD) is a familial neurodegenerative disorder with genetic features usually associated with aging that continues to worsen after it is diagnosed. The extrapyramidal motor deficits (resting tremor, muscular rigidity, etc.) are a result of the large spread reduction in dopamine levels in the striatum (Child et al., 2024), etc., due to the degeneration of dopamine-producing perikarya in the pars compacta of the substantia nigra in the mesencephalon (van Munster et al., 2024). The bulk of the evidence indicates that PD is a consequence of misfolded proteins such as α-synuclein, ubiquitin and other proteins, that form by involving prion-like processes. Increasing amounts of α-synuclein accumulate intracellularly as aggregates referred to as Lewy bodies which increase the vulnerability of neurons to morphological and physiological degradation (Li et al., 2024a). A number of genes have been identified (Fig.5) that assist in the development of PD with their excessive expression promoting mitochondrial ROS which causes mtDNA damage which subsequently induces the faulty transcription of critical proteins of the ETC, reducing complex IV activity and compromising ATP production. The pathological changes which included exaggerated oxidative stress, faulty molecular trafficking, ETC deficiencies, perturbed matrix Ca^{2+} homeostasis, etc., all involve severe mitochondrial disturbances. Associated with these changes is a promotion of neuroinflammation, a condition that is also associated with proinflammatory cytokine-mediated ROS generation (Scarian et al., 2024). Many studies have documented the mitochondrial protective effects of melatonin in PD (Diaz-Casado et al., 2016; Patki and Lau, 2011; Wongprayoon and Govitrapong, 2017). Among these, major improvements attributed to melatonin include enhanced mitochondrial respiration, improved mitochondrial dynamics, increased ATP generation, elevated antioxidant enzyme levels, and strengthened anti-apoptotic activities.

Perturbations in glucose processing in PD neurons is also common and a correction of this deficiency is considered a potential therapy for PD (Yang et al., 2024; Zhang et al., 2011). Interestingly, in contrast to what occurs in cancer cells, in neurodegenerative diseases where glycolysis prevails, it is accompanied by reduced cellular respiration, lower energy stores and exaggerated apoptosis which helps to explain the neurobehavioral and cognitive losses. In tumor cells, Warburg metabolism supports cellular proliferation and survival (Pacini and Borziani, 2016). This dichotomy of actions of melatonin is shared by other molecules, e.g., dichloroacetate, α-lipoic acid, etc., in reference to neurodegenerating and cancer cells which act similarly.

The central neurons of other age-related neurodegenerative diseases exhibit many similar aberrant energetic and metabolic changes that occur in AD and PD. Huntington disease (HD) is rare genetic progressive neurological condition that is manifested as involuntary movements (chorea), cognition difficulties and psychiatric disturbances (Sawant et al., 2024). Mental confusion, exaggerated moods, inability to concentrate, and difficulty in understanding are among the many features of this debilitating condition. HD is a result of the huntingtin gene mutation (mHtt) which causes cytosine, adenine and guanine (CAG) to be excessively repeated in DNA (Fig.5). While HD *per se* does not shorten life span, the afflicted individuals often die prematurely from other causes. Melatonin's neuroprotective effects against neurotoxicity in HD is primarily due to its antioxidant properties. While attenuating neuronal cell death, it also restores mitochondrial enzyme activities and prevents reduction in GSH levels (Wongprayoon and Govitrapong, 2017). A recent study by Kim and co-workers (2023) showed that expression of AANAT, the rate-limiting enzyme in the melatonin synthesis, is significantly reduced in the pineal gland and the striatum of HD patients. Using R6/2 mouse model of HD, AANAT expression was proven to be particularly reduced in synaptosomal mitochondria.

HD patients have an upregulation of the canonical WNT/β-catenin signaling pathway which activates the mitochondrial pyruvate dehydrogenase kinase-1 (PDK-1) enzyme which inhibits PDC preventing the intramitochondrial formation of acetyl CoA. β-Catenin is upregulated as a result of the inhibition of its phosphorylation which prevents its proteosomal degradation (Vallee et al., 2018). With the suppression of PKC,

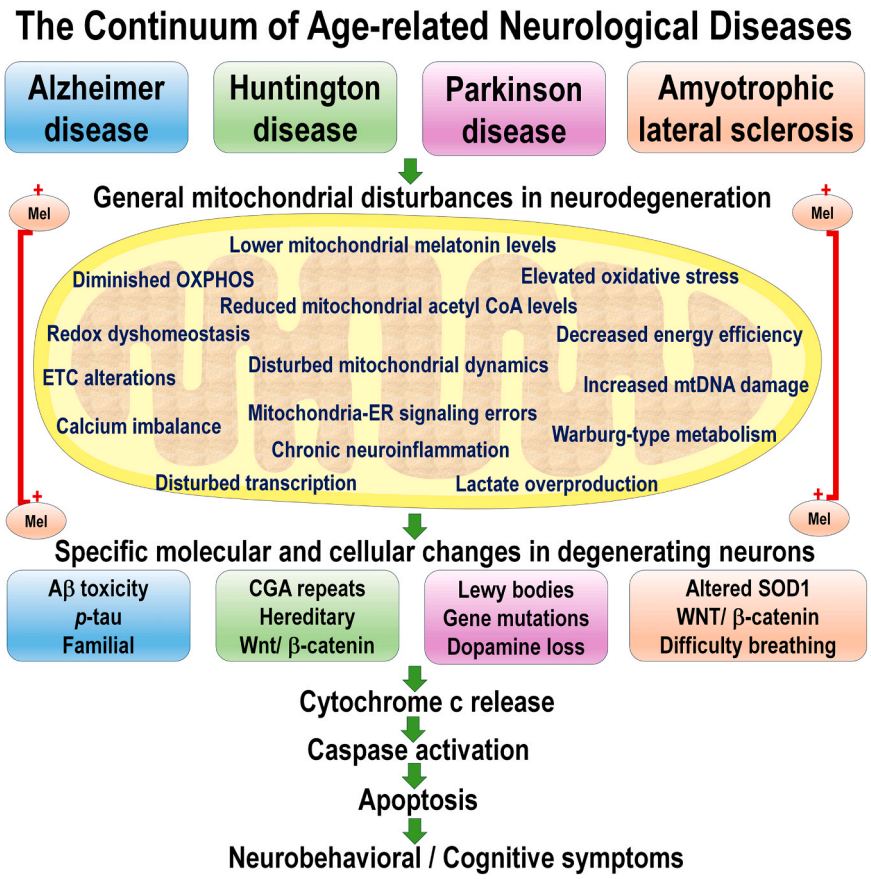

Fig. 5. This flow diagram summarizes the metabolic disturbances in the four neurodegenerative diseases discussed in this report. While the specific causes of the diseases differ, the mitochondrial perturbations that occur are similar primarily because of the shift from mitochondrial OXPHOS to Warburg-type metabolism (changes listed overlying the mitochondrion). Also, there is significant overlap regarding the specific morphological phenotypes the conditions display and not all the specific features of each disease are listed. Melatonin switches pathological cells from Warburg-type metabolism, possibly by inhibiting hypoxia inducible factor-1α (HIF-1α) (not shown in the figure). This switch in the metabolic phenotype may be part of the explanation by which the indole modulates the course of these and other diseases. In addition to correcting the mitochondrial deficiencies (represented by the brackets associated with the mitochondrion and the symbol, +MEL), there is also evidence that melatonin reduces Aβ and phosphorylated tau (p-tau) accumulation, and blocks Lewy body (α-synuclein) formation.

the affected neurons adopt aerobic glycolysis (Warburg-type metabolism) with the elevated generation of the fermentation product, lactate, and a shift away from OXPHOS (Sameni et al., 2016). Thus, HD neurons select glycolysis for the inefficient but rapid production of ATP, as do many other pathological cells, with mitochondrial OXPHOS playing a secondary role in energy generation. This metabolic shift is typical reversed by melatonin in other cells.

Amyotrophic lateral sclerosis (ALS) is a progressive neurological disorder that is associated with both upper (precentral gyrus) and lower (anterior column neurons) motoneuron degeneration. Consequently, ALS patients exhibit pronounced muscle weakness that culminates is muscle atrophy. The most frequent cause of death is respiratory failure due to the weakened muscles surrounding the thoracic cavity. AS has both genetic (10 % familial and 90 % sporadic) and environmental factors as being causative (Couratier et al., 2021). Multiple genes are related to the development of ALS, the most common of which are superoxide dismutase 1 (Cu, ZnSOD), TAR DNA-binding protein, fused in sarcoma and chromosome 9 open reading frame 72 (Fig. 5) (Mead et al., 2023). The loss of neurons in ALS is triggered by mitochondrial dysfunction which includes the over production of ROS (Roy et al., 2024), a pathological hallmark of the disease, which leads to mitochondrial DNA mutations that eventually cause these organelles to functionally implode. The neuroprotective effect of melatonin has been documented in transgenic ALS mice (Zhang et al., 2013), evidenced by the prevention of neurological deterioration and delayed disease onset. At the molecular level, melatonin counteracted apoptosis by inhibiting caspase-3 and Rip2/caspase-1, and by blocking mitochondrial cytochrome c release. These effects were observed in the spinal cord of ALS mice and were mediated by the MT1 receptor.

Disrupted energy production is a potential factor that supports the development of ALS ALS is accompanied by a reduction in both OXPHOS and ATP generation since these cells preclude mitochondrial pyruvate-derived acetyl CoA synthesis when they adopt the glycolytic phenotype due to the inhibition of PDC. Drugs, such as dichloroacetate, that directly or indirectly inhibit PDK, the suppressor of PDC, causes disinhibition of the latter enzyme with the re-establishment of an improved mitochondrial function with reduced ROS formation and oxidative stress; this is an action shared by melatonin.

The ability of melatonin to reverse Warburg-type metabolism, often referred to as a glycolytic metabolism, in aberrantly functioning cells may be a critical factor in its ability to inhibit these pathologies (Reiter et al., 2020). Indeed, a number of authors have mentioned that reversing Warburg-type metabolism may be an important means of deferring the progression of pathologies such as cancer and neurodegenerative diseases (Grimm et al., 2016; Yang et al., 2017). This abnormal type of metabolism, which was initially described in cancer tissue, is now known to occur in many pathological cells (Reiter et al., 2021b).

Warburg-type metabolism provides pathological cells with metabolic advantages that are used to advance the tissue destruction and cell death. Glycolysis is associated with acidification of the cellular microenvironment which surely impacts the physiology of the associated cells. For example, relative to cancer cells the acidic environment supports the

ingrowth of blood vessels as well as tumor invasion and metastasis (Chen et al., 2024a). Also, switching from glycolysis to mitochondrial OXPHOS typically reduces free radical generation by the ETC, thereby also limiting local molecular damage, including the destruction of mtDNA (Reiter et al., 2022). This lowers the inaccurate transcription of proteins that serve as enzymes in the ETC and reduces the number of electrons that are leaked from the ETC so the quantity of chemically reduced oxygen molecules (ROS) produced is diminished, thus lowering the total oxidative load of the mitochondria (Fig. 5).

In addition to these actions, promoted by melatonin, which enhance the ability of mitochondria to passively protect themselves from ROS-mediated damage, there are also other direct means that assist these multifunctionally organelles in being protected from excessive free radical damage and malfunction. When pyruvate is prevented from entering the mitochondria to be converted to acetyl CoA due to the inhibition of PDC by the elevated activity of PDK, acetyl CoA levels are diminished. This has a negative effect on the citric acid cycle and on fluent OXPHOS. Additionally, since acetyl CoA is a necessary co-substrate in the melatonin synthetic pathway, its reduction also lowers the levels of this important mitochondrial antioxidant which allows any ROS produced to mutilate adjacent molecules without interference. In pathological cells manifesting Warburg-type metabolism the intracellular melatonin concentrations are known to be reduced by roughly 50 % (Cucielo et al., 2023; Gaiotte et al., 2022). Melatonin and its metabolites are not only highly efficient and directly involved in the detoxification of ROS/RNS, melatonin also promotes the synthesis of another highly important intramitochondrial radical scavenger, glutathione, by regulating its synthesis (Li et al., 2019). Moreover, via the SIRT3 pathway, melatonin upregulates mitochondrial SOD2 (Pi et al., 2015) (Fig. 4); the activity of this antioxidative enzyme is critical in limiting oxidative stress in the mitochondria and preventing cellular apoptosis (Jiao et al., 2023).

When melatonin is used to treat animals or humans bearing tumors, it reverses Warburg-type metabolism and limits tumor progression (Blask et al., 2014; Li et al., 2021). Although there are other means by which melatonin may potentially restore mitochondria acetyl CoA production, current thought is that melatonin administration suppresses HIF-1α, which in turn reduces the activity of PDK4 which disinhibits PDC allowing for the intramitochondrial synthesis of acetyl CoA (Fig. 3) (Reiter et al., 2022). This supports local melatonin production and is a critical factor in stabilizing mitochondrial functional homeostasis. Other molecules that reverse Warburg-type metabolism, e.g., dichloroacetate, that have similar effects in recovering mitochondrial physiology and inhibiting pathological cells probably work similar to melatonin, although those studies have never considered the importance of intramitochondrial melatonin production (Feng et al., 2023). Thus, considering the efficacy of melatonin in reducing glycolysis and ensuring optimal mitochondrial physiology as well as OXPHOS via the enhancement of mitochondrial melatonin levels, we propose it as a means by which melatonin alters the onset or progression of neurodegenerative diseases as outlined in the current report.

7. Mitochondrial transfer and extracellular mitochondrial signaling in CNS disorders

As already established, mitochondria participate in perhaps every cellular function that normally occurs. Thus, the disruption of mitochondrial physiology has a disproportional negative effect on cell metabolism and survival. Consequently, it is imperative that these organelles be maintained in an optimally functional state. Certainly, as summarized herein, the presence of the multifunctional antioxidant, melatonin, in the mitochondria could be a major factor in preserving the many critical functions of these organelles by reducing the oxidative damage that these organelles sustain on a daily basis. Any agent that prevents or restores mitochondrial function would play a major role in supporting cellular health and ensuring improved functioning of the aging organism.

Recent evidence indicates that undamaged normal mitochondria may be capable of being horizontally transferred from a healthy to a damaged cell thereby aiding in recovery of the functionally distressed cell. One means by which mitochondria are moved among cells is via tunneling nanotubes (TNT). TNT are nano-sized membranous conduits that form between cells (often between normal and damaged cells); they are filled with cytosolic elements including cytoskeletal filaments, especially F-actin. F-actin is involved in the formation of TNT, and it also supports the transport of mitochondria between cells via these tubular structures. One of the major means governing the movement of mitochondria between cells via the TNT has been described as involving mitochondrial Rho GTPase 1 (Miro1) which acts as a calcium-sensitive motor-protein (Domhan et al., 2011). The transport of mitochondria and other cytosolic elements via TNT has been observed between multiple cell types with the exchange of healthy mitochondria aiding in the functional restoration of the damaged recipient cell and supporting tissue regeneration (Liu et al., 2023; Luchetti et al., 2023; Reiter et al., 2022).

That melatonin improves mitochondrial transfer between cells via TNT has been amply documented in two recent reports (Nasoni et al., 2021; Yip et al., 2021). In a combined *in vitro/in vivo* investigation, Yip and co-workers found that pretreating mitochondria with melatonin enhanced their transfer between cells, increased the antioxidative capacity and reduced apoptosis of the recipient cells (Yip et al., 2021). In the *in vivo* investigation, they observed a reduction in induced brain infarct size and improved neurological outcomes as estimated by the measurement of a lower frequency of neuronal apoptosis and autophagy, improved resistance against oxidative damage and decreased DNA damage in the recovering cells. Also using a model of ischemia/reoxygenation damage of hippocampal HT22 cells, Nasoni and colleagues (Nasoni et al., 2021) reported that melatonin treatment augmented mitochondrial transfer from normal to damaged neurons via TNT and improved a host of physiological and molecular parameters in the ischemic/reperfused neurons. Evidence that the health status of the mitochondria was improved was supported by the higher expression of the membrane translocase proteins, TOM20 and TIM23, and of the mitochondrial matrix protein, HSP60. Moreover, mitochondrial fusion improved due to the upregulation MFN2 and OPA1. Furthermore, Nasoni and colleagues confirmed that mitochondrial were actually transferred between undamaged and damaged neurons by using Mitotracker Deep Red mitochondrial dye (Nasoni et al., 2021). Obviously, the relocation of healthy mitochondria to functionally compromised cells would be beneficial due to the greater availability of energy in terms of ATP abundance but also likely as result of the increased availability of the antioxidant melatonin, which is believed to be formed in normally functioning neuronal mitochondria (Suofu et al., 2017). Oxidative stress is a major contributor to cellular death that occurs in ischemic/re-perfused tissues with melatonin reducing oxidative damage and allowing cells to recover by promoting anastasis (Reiter et al., 2022).

In addition to being moved between cells in TNT, recent evidence has shown that active mitochondria are actually discharged from cells into the extracellular environment from where they enter the blood. The secretion of mitochondria by various cells results due to a variety of different stimuli including inflammation and elevated stress. The extruded mitochondria are internalized by other cells via endocytosis, macro-pinocytosis and/or integrin-dependent pathways (Hayakawa et al., 2016). Mitochondria are also moved between cells by means of exosomes (Park and Hayakawa, 2021). There is a substantial amount of data showing that melatonin impacts exosome formation and release. Finally, there is evidence that information-containing vesicles from mitochondria in one cell can directly migrate to adjacent cells to signal their mitochondria (Shen et al., 2022a). Whether melatonin, by these various means, has any effect of mitochondrial information transfer between cells remains to be investigated (Novais et al., 2021).

8. Conclusions and perspectives

While the current review focuses on the role of melatonin as an antioxidant in determining brain aging, it is in fact a multitasking molecule which has other actions that contribute to its ability to delay neurological deterioration (Reiter et al., 2010). The senescence-accelerated mouse-prone 8 (SAMP8), which exhibits oxidative-mediated accelerated loss of neural function, is a valuable model to study brain aging. When these animals were treated with melatonin daily, not only was the total neural oxidative burden reduced but also amyloid and tau-related pathologies were delayed; these protections against brain aging were associated with a marked rise in the expression of sirtuin 1 (SIRT1) (Cristofol et al., 2012). Both melatonin and caloric restriction, a well-known inhibitor of aging, upregulated mRNA expression of the SIRT1/FoxO pathway and proteins involved in cell cycle regulation in the mouse hippocampus (Jenwitheesuk et al., 2018). Both treatments individually also protected against brain aging, but the effects were not additive when the treatments were combined. There are many other reports documenting the ability of melatonin to reduce the severity of neurodegenerative diseases which are only indirectly related to its free radical scavenging activity; some of these actions as they relate to Alzheimer's disease are summarized in Fig. 4 (Shukla et al., 2017).

Inflammation is also a major player in age-related morphophysiological cognitive loss and in most neurodegenerative diseases (Chand Dakal et al., 2024). There is abundant evidence that this is mediated by activation and assembly of the NLPR3 inflammasome, in part a consequence of excessive ROS generation in the mitochondria (mtROS) and radical species generated by oxidases. NLPR3 stimulates caspase 1 which induces the release of proinflammatory cytokines, interleukin 18 and interleukin 1β, which further aggravates ROS production in already damaged mitochondria including those in neurons (Blevins et al., 2022). Also mitophagy, which would rid neurons of dysfunctional mitochondria, negatively correlates with the activation of inflammasome (Nakahira et al., 2011). Melatonin is a known inhibitor of inflammation due to its prevention of NF-κB translocation into the nucleus, reducing the activation of the inflammasome by regulating mtROS production, stimulating the KEAP/Nrf2 pathway and promoting mitophagy (Bocheva et al., 2024; Lewis Lujan et al., 2022; Vriend and Reiter, 2015b; Wang et al., 2022). This combination of actions surely contributes to melatonin's anti-inflammatory and antiaging effects in the central nervous system.

Endoplasmic reticulum (ER) has critical roles in determining the quality of protein synthesis in neurons. ER stress triggers an adaptive change known as the unfolded protein response (UPR) which can either induce cell death or recover cellular homeostasis (Gow and Sharma, 2003; Shi et al., 2018). The regulation of the UPR by melatonin involves its ability to modulate mitochondrial oxidative stress, to downregulate inflammation, to repair molecular damage, and to prevent cellular loss by reducing apoptosis (de Almeida Chuffa et al., 2024). ER stress and the associated UPR is a common feature of neurodegeneration when the mutilated protein forms aggregates that negatively impact neuronal function (Yoo and Joo, 2023). Melatonin, due to its multiple functions including the downregulation of CHOP and attenuating PERK and GRP78/BiP, reduces neuronal apoptosis that accompanies the UPR; this limits the loss of functional neurons.

In the CNS, the locus coeruleus (LC), a small nucleus located bilaterally in the pons, is the primary site of norepinephrine (NE) synthesis, with the axons of these neurons distributing this neurotransmitter throughout most of the brain. Damage to the LC and its projections are reportedly related to dementia, depression, and include AD and PD pathologies (Fig. 4) (Nikolenko et al., 2024; Thangwaritorn et al., 2024). Also relative to AD, changes in acetylcholine (Ach) have been proposed as a causative agent (Ferreira-Vieira et al., 2016). Cholinergic neurons are located in several areas of the brain but especially in the nucleus basalis of Meynert (Woolf and Butcher, 2011). In organotypic brain slices, melatonin with nerve growth factor preserved the number of ACh neurons in the nucleus basalis but the study did not examine the ACh synthetic activity of the neurons. The evidence is meager that melatonin can restore either neural NE or ACh levels in the brain undergoing late life degeneration. It is known that blood and CSF melatonin levels drop in the elderly (Nous et al., 2021; Sack et al., 1986; Scholtens et al., 2016) when the brain is afflicted with the loss of functional neurons, but it seems these concurrent changes are merely coincidental. Likewise, while NE is key neurotransmitter that upregulates melatonin production in the pineal gland (Hertz et al., 2020), there is no data showing that NE stimulates melatonin synthesis in neuronal mitochondria anywhere in the CNS. Since sleep deprivation is a significant risk factor for AD, the depressed nocturnal increase in melatonin which promotes healthy sleep could be an indirect critical factor in determining the rate of progression of neurodegenerative conditions (Akyuz et al., 2024).

Type 3 diabetes is a term that is associated with Alzheimer's neural degeneration (Xie et al., 2023). Insulin, which controls blood glucose levels and its uptake and metabolism by tissues, is especially important for brain physiology because of the high dependence of neural tissue on glucose. Glucose is essential for cell growth, their differentiation, and it supports protein synthesis. Conversely, glucose interferes with glycolysis and protein catabolism. Receptors for insulin and insulin-like growth factor-1 are widely distributed in the central nervous system and because they support glucose uptake as elsewhere, they are essential for cognitive functions and influencing the uptake of norepinephrine and other neurotransmitters. Insulin resistance, which occurs in Alzheimer's disease neurons (AD), hastens the rate of neurodegeneration (Albar et al., 2024). AD neurons are insulin insensitive which is reversed by melatonin treatment thereby causing a delay of AD progression (Shen et al., 2022b). Several neurodegenerative diseases including AD also exhibit Warburg type metabolism (Yang et al., 2024), which is additionally reversed by melatonin which aids in stalling neurological decline (Reiter et al., 2021b). These and other actions of melatonin in limiting neurodegenerative pathology in AD are summarized in Fig. 4.

Melatonin and its derivatives have complex molecular interactions within cells since there are both receptor-independent functions and receptor-dependent processes. The potent actions of melatonin and its metabolites in reducing neural oxidative stress likely involves both receptor-independent and receptor dependent mechanism. As direct scavengers these multipurpose antioxidants neutralize ROS/RNS by electron or hydrogen transfer and radical adduct formation (Galano and Reiter, 2018) with some of the metabolites of melatonin being more efficient scavengers than melatonin itself. In addition, melatonin, in particular, chelates transition metals to reduce the formation of the highly damaging ·OH and enhances molecular repair. In addition to directly detoxifying reactive species, melatonin stimulates antioxidative enzymes, e.g., superoxide dismutase, glutathione synthetase, glutathione reductase, etc., and inhibits prooxidant enzymes, with the likely involvement of melatonin receptors (Galano et al., 2018). Melatonin receptors are widely distributed throughout the CNS with their density differing according to the specific nuclear group.

Membrane melatonin receptors have been pharmacologically characterized and cloned and are widely, albeit seemingly unevenly distributed in the CNS (Glatfelter et al., 2021; Reppert, 1997). The major receptors for melatonin are G-protein coupled receptors and classified as MT1 and MT2 with the signal transduction mechanisms being well described (Okamoto et al., 2024). Additionally, there are potential cytosolic melatonin receptors/binding sites, i.e., quinone reductase (sometimes referred to as MT3) and calmodulin (Benitez-King et al., 2024; Boutin, 2016). In the nucleus, the orphan receptor RORα binds melatonin, an action that is not shared by RORβ (Panmanee et al., 2024; Wu et al., 2024).

Even though numerous binding sites for melatonin have been unveiled, which of these are involved in mediating the specific shielding actions of melatonin against age-related neurodegeneration have not been defined. Most of what is known about receptor mediated actions of

melatonin relate to the MT1 and MT2 receptors on the cell surface. The presence of the MT1 receptor on the mitochondrial membrane, as recently discovered, however, may be highly relevant in safeguarding this critical organelle from degradation (Suofu et al., 2017). The study in question showed that the melatonin receptor on the mitochondrial membrane is associated with β-arrestins and a G-protein. Melatonin synthesized in the mitochondrial matrix is released into the cytosol and acts via the MT1 signaling pathway to suppress caspase upregulation and stress-enhanced cytochrome c release from the mitochondria. In the same report, the authors observed an overexpression on the MT1 receptor in the ischemic mouse brain and concluded that the beneficial effects of melatonin on this neural assault are mediated by its action on the mitochondrial MT1 receptor; this is the best evidence to date that the ability of melatonin to limit neural decline in the aged may, in part, involve its mitochondrial membrane receptor-mediated actions. Since exogenously administered melatonin readily crosses the blood-brain barrier and enters neurons, supplemental melatonin in late life could also defer cognitive decline via the same mechanism (Huo et al., 2017; Iwashita et al., 2021; Mayo et al., 2018).

Endogenous melatonin levels steadily decline during aging and in elderly individuals, the levels are often a fraction of what they were when these subjects were young. The loss of the protection afforded by melatonin has often been suggested as a contributory factor to neural degeneration. Numerous experimental studies have documented that essentially all aspects of neuronal mitochondrial function benefit from the presence of melatonin and, in contrast, mitochondrial dysfunction is likely a major contributor to age-related biobehavioral deterioration and dementia. In numerous experimental models, giving melatonin exogenously has been shown repeatedly to attenuate the progression or severity of experimental Alzheimer's disease, parkinsonism, amyotrophic lateral sclerosis, etc. Given these findings, some consideration should be given to supplementing the aging population with melatonin; since these insidious diseases are initiated many years before the overt signs are apparent and a diagnosis is made, the preventative treatment should begin well in advance of the diagnosis. Certainly, prevention is always better than treatment. These clinical investigations should strive to identify the optimal efficacious dose and compare the different routes of administration.

Neurodegenerative diseases are occurring with increasing frequency because of the longer life of many individuals. Neurodegeneration is a major cause of morbidity and mortality in the older population, and these are devastating diseases for individuals, families and social welfare systems. Besides the toll on human dignity, etc., financially these conditions are expensive to treat creating a major problem for all involved. To begin treatment after the diagnosis is made would be expected to be imminently less successful than initiating treatment in advance of the first appearance of disease signs. As practical as this approach would seem to be, chronically treating humans with fabricated, and often expensive, medications that commonly have undesired effects for a disease a subject may never get is highly problematic. In light of this, supplementing with melatonin, which is inexpensive and safe, may be a acceptable means of slowing the degenerative processes and in some cases preventing the condition. Considering the overwhelming costs for the treatment of these conditions, the use of melatonin may be fiscally judicious. Even short-term delays in the progression of these diseases would prove of extreme importance and prolong the dignity and welfare, and financial resources, of those involved. To reiterate, the use of melatonin to defer mitochondrial aging may prove to be a significant benefit in altering the trajectory of neurodegenerative disease progression. The risk of not using melatonin in the long term by the aging population for the purpose of potentially slowing the development or reducing the severity of cognitive decline may prove to be a much more expensive and physiologically debilitating than avoiding its use.

The safety of melatonin for regular use is well established. Moreover, it is normally an endogenously synthesized molecule in all species including vertebrates, invertebrates and plants. Thus, taking supplemental melatonin does not introduce a foreign molecule, such as a prescription drug, into the system. All organisms have processed melatonin and utilized it to regulate their metabolism throughout life. Indeed, its loss seems to be a factor in functional failure of mitochondrial physiology including energy production (ATP) in the aged. Mitochondrial failure is a common feature of aging cells., not only of neurons but of all cells. Finally, based on data from numerous scientific reports including studies in humans, the use of melatonin, in what are considered to be pharmacological doses, seems not to be a major issue given the very large, documented safety margin of melatonin.

Multiple questions related to how mitochondria fit into the entire scheme of cellular physiology and aging obviously remain. What is certain is that the function of these organelles far exceeds what has been historically thought. The more research that is performed on these functionally intertwined organelles, the more questions that are uncovered. This complexity is made even more enigmatic with the discovery of a multifunctional molecule, melatonin, in the organelle. Many of the functions for which mitochondria are responsible also are impacted by melatonin, e.g., redox homeostasis, immune physiology, metabolism, apoptosis regulation, mitochondrial dynamics, signaling among different cellular organelles, etc. Uncovering all the interactions related to mitochondria and melatonin is required if we are to understand the pathophysiology of age-associated neural diseases and organismal aging itself. As new data are unveiled, it will be important to leverage this information in the design of appropriate therapeutics to defer the signs of aging, i.e., prolong health span.

CRediT authorship contribution statement

Conceptualization, RJR, WM; identifying and curation of published literature, RS, LGC, DGS, SRC; writing original version of the manuscript, RJR, WM, SRC, LGC, DL, FL, WB, PG; reading and editing the manuscript, RS, LGC, DGS, SRC, PG; figure preparation, RS.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

No data was used for the research described in the article.

Acknowledgements

Supported, in part, by funding from the Rowe-Smith Foundation.

References

Acuna-Castroviejo, D., Escames, G., Venegas, C., Diaz-Casado, M.E., Lima-Cabello, E., Lopez, L.C., Rosales-Corral, S., Tan, D.X., Reiter, R.J., 2014. Extrapineal melatonin: sources, regulation, and potential functions. Cell. Mol. Life Sci. 71, 2997–3025. https://doi.org/10.1007/s00018-014-1579-2.

Acuña-Castroviejo, D., Noguiera-Navarro, M.T., Reiter, R.J., Escames, G., 2018. Melatonin actions in the heart; more than a hormone. Melatonin Res. 1, 21–26. https://doi.org/10.32794/mr11250002.

Ahammed, G.J., Li, Z., Chen, J., Dong, Y., Qu, K., Guo, T., Wang, F., Liu, A., Chen, S., Li, X., 2024. Reactive oxygen species signaling in melatonin-mediated plant stress response. Plant Physiol. Biochem 207, 108398. https://doi.org/10.1016/j.plaphy.2024.108398.

Akbar, M., Essa, M.M., Daradkeh, G., Abdelmegeed, M.A., Choi, Y., Mahmood, L., Song, B.J., 2016. Mitochondrial dysfunction and cell death in neurodegenerative diseases through nitroxidative stress. Brain Res 1637, 34–55. https://doi.org/10.1016/j.brainres.2016.02.016.

Akyuz, E., Arulsamy, A., Aslan, F.S., Sarisozen, B., Guney, B., Hekimoglu, A., Yilmaz, B. N., Retinasamy, T., Shaikh, M.F., 2024. An expanded narrative review of neurotransmitters on Alzheimer's disease: the role of therapeutic interventions on neurotransmission. Mol. Neurobiol. https://doi.org/10.1007/s12035-024-04333-y.

Albar, N.Y., Hassaballa, H., Shikh, H., Albar, Y., Ibrahim, A.S., Mousa, A.H., Alshanberi, A.M., Elgebaly, A., Bahbah, E.I., 2024. The interaction between insulin

resistance and Alzheimer's disease: a review article. Postgrad. Med. 136, 377–395. https://doi.org/10.1080/00325481.2024.2360887.
Alvarez-Diduk, R., Galano, A., Tan, D.X., Reiter, R.J., 2015. N-acetylserotonin and 6-hydroxymelatonin against oxidative stress: implications for the overall protection exerted by melatonin. J. Phys. Chem. B. 119, 8535–8543. https://doi.org/10.1021/acs.jpcb.5b04920.
Andre-Levigne, D., Pignel, R., Boet, S., Jaquet, V., Kalbermatten, D.F., Madduri, S., 2024. Role of oxygen and its radicals in peripheral nerve regeneration: from hypoxia to physoxia to hyperoxia. Int. J. Mol. Sci. 25, 2030. https://doi.org/10.3390/ijms25042030.
Andrieux, P., Chevillard, C., Cunha-Neto, E., Nunes, J.P.S., 2021. Mitochondria as a cellular hub in infection and inflammation. Int. J. Mol. Sci. 22, 11338. https://doi.org/10.3390/ijms222111338.
Anghel, L., Baroiu, L., Popazu, C.R., Patras, D., Fotea, S., Nechifor, A., Ciubara, A., Nechita, L., Musat, C.L., Stefanopol, I.A., Tatu, A.L., Ciubara, A.B., 2022. Benefits and adverse events of melatonin use in the elderly (Review). Exp. Ther. Med. 23, 219. https://doi.org/10.3892/etm.2022.11142.
Anisimov, V.N., 2003. Effects of exogenous melatonin–a review. Toxicol. Pathol. 31, 589–603. https://doi.org/10.1080/01926230390257885.
Azbarova, A.V., Knorre, D.A., 2023. Role of mitochondrial DNA in yeast replicative aging. Biochemistry 88, 1997–2006. https://doi.org/10.1134/S0006297923120040.
Barba, I., Carrillo-Bosch, L., Seoane, J., 2024. Targeting the warburg effect in cancer: where do we stand? Int. J. Mol. Sci. 25, 3142. https://doi.org/10.3390/ijms25063142.
Bartman, S., Coppotelli, G., Ross, J.M., 2024. Mitochondrial dysfunction: a key player in brain aging and diseases. Curr. Issues Mol. Biol. 46, 1987–2026. https://doi.org/10.3390/cimb46030130.
Benitez-King, G., Argueta, J., Miranda-Riestra, A., Munoz-Delgado, J., Estrada-Reyes, R., 2024. Interaction of the melatonin/Ca(2+)-CaM complex with calmodulin kinase ii: physiological importance. Mol. Pharmacol. 106, 3–12. https://doi.org/10.1124/molpharm.123.000812.
Benot, S., Goberna, R., Reiter, R.J., Garcia-Maurino, S., Osuna, C., Guerrero, J.M., 1999. Physiological levels of melatonin contribute to the antioxidant capacity of human serum. J. Pineal Res. 27, 59–64. https://doi.org/10.1111/j.1600-079x.1999.tb00597.x.
Bhattacharya, A., Chakraborty, M., Chanda, A., Alqahtani, T., Kumer, A., Dhara, B., Chattopadhyay, M., 2024. Neuroendocrine and cellular mechanisms in stress resilience: From hormonal influence in the CNS to mitochondrial dysfunction and oxidative stress. J. Cell Mol. Med 28, e18220. https://doi.org/10.1111/jcmm.18220.
Bianchet, M.A., Erdemli, S.B., Amzel, L.M., 2008. Structure, function, and mechanism of cytosolic quinone reductases. Vitam. Horm. 78, 63–84. https://doi.org/10.1016/S0083-6729(07)00004-0.
Bianchi, C., Martinelli, R.P., Rozados, V.R., Scharovsky, O.G., 2024. Use of sodium dichloroacetate for cancer treatment: a scoping review. Medicina 84, 313–323.
Blask, D.E., Dauchy, R.T., Dauchy, E.M., Mao, L., Hill, S.M., Greene, M.W., Belancio, V.P., Sauer, L.A., Davidson, L., 2014. Light exposure at night disrupts host/cancer circadian regulatory dynamics: impact on the Warburg effect, lipid signaling and tumor growth prevention. PLoS One 9, e102776. https://doi.org/10.1371/journal.pone.0102776.
Blevins, H.M., Xu, Y., Biby, S., Zhang, S., 2022. The NLRP3 inflammasome pathway: a review of mechanisms and inhibitors for the treatment of inflammatory diseases. Front. Aging Neurosci. 14, 879021 https://doi.org/10.3389/fnagi.2022.879021.
Bocheva, G., Bakalov, D., Iliev, P., Tafradjiiska-Hadjiolova, R., 2024. The vital role of melatonin and its metabolites in the neuroprotection and retardation of brain aging. Int. J. Mol. Sci. 25, 5122. https://doi.org/10.3390/ijms25105122.
Boutin, J.A., 2016. Quinone reductase 2 as a promising target of melatonin therapeutic actions. Expert Opin. Ther. Targets 20, 303–317. https://doi.org/10.1517/14728222.2016.1091882.
Bromme, H.J., Morke, W., Peschke, E., 2002. Transformation of barbituric acid into alloxan by hydroxyl radicals: interaction with melatonin and with other hydroxyl radical scavengers. J. Pineal Res. 33, 239–247. https://doi.org/10.1034/j.1600-079x.2002.02936.x.
Bruce, J., Tamarkin, L., Riedel, C., Markey, S., Oldfield, E., 1991. Sequential cerebrospinal fluid and plasma sampling in humans: 24-hour melatonin measurements in normal subjects and after peripheral sympathectomy. J. Clin. Endocrinol. Metab. 72, 819–823. https://doi.org/10.1210/jcem-72-4-819.
Burns, J.S., Manda, G., 2017. Metabolic pathways of the warburg effect in health and disease: perspectives of choice, chain or chance. Int. J. Mol. Sci. 18, 2755. https://doi.org/10.3390/ijms18122755.
Cardinali, D.P., 2024. Melatonin as a chronobiotic/cytoprotective agent in bone. Doses involved. J. Pineal Res. 76, e12931 https://doi.org/10.1111/jpi.12931.
Carey, J.L., Guo, L., 2022. Liquid-liquid phase separation of TDP-43 and FUS in physiology and pathology of neurodegenerative diseases. Front Mol. Biosci. 9, 826719 https://doi.org/10.3389/fmolb.2022.826719.
Chand Dakal, T., Choudhary, K., Tiwari, I., Yadav, V., Kumar Maurya, P., Kumar Sharma, N., 2024. Unraveling the triad: hypoxia, oxidative stress and inflammation in neurodegenerative disorders. Neuroscience 552, 126–141. https://doi.org/10.1016/j.neuroscience.2024.06.021.
Chawla, S., O'Neill, J., Knight, M.I., He, Y., Wang, L., Maronde, E., Rodriguez, S.G., van Ooijen, G., Garbarino-Pico, E., Wolf, E., Dkhissi-Benyahya, O., Nikhat, A., Chakrabarti, S., Youngstedt, S.D., Zi-Ching Mak, N., Provencio, I., Oster, H., Goel, N., Caba, M., Oosthuizen, M., Duffield, G.E., Chabot, C., Davis, S.J., 2024. Timely questions emerging in chronobiology: the circadian clock keeps on ticking. J. Circadian Rhythms 22, 2. https://doi.org/10.5334/jcr.237.
Chen, C., Yang, C., Wang, J., Huang, X., Yu, H., Li, S., Li, S., Zhang, Z., Liu, J., Yang, X., Liu, G.P., 2021. Melatonin ameliorates cognitive deficits through improving mitophagy in a mouse model of Alzheimer's disease. J. Pineal Res. 71, e12774 https://doi.org/10.1111/jpi.12774.
Chen, S., Xu, Y., Zhuo, W., Zhang, L., 2024a. The emerging role of lactate in tumor microenvironment and its clinical relevance. Cancer Lett. 590, 216837 https://doi.org/10.1016/j.canlet.2024.216837.
Chen, T., Xie, Q., Tan, B., Yi, Q., Xiang, H., Wang, R., Zhou, Q., He, B., Tian, J., Zhu, J., Xu, H., 2024b. Inhibition of pyruvate dehydrogenase kinase 4 protects cardiomyocytes from lipopolysaccharide-induced mitochondrial damage by reducing lactate accumulation. Inflammation. https://doi.org/10.1007/s10753-024-01981-z.
Child, B., Saywell, I., da Silva, R., Collins-Praino, L., Baetu, I., 2024. Cognitive function in different motor subtypes of Parkinson's disease: A systematic review protocol. Health Sci. Rep. 7, e2092 https://doi.org/10.1002/hsr2.2092.
Couratier, P., Lautrette, G., Luna, J.A., Corcia, P., 2021. Phenotypic variability in amyotrophic lateral sclerosis. Rev. Neurol. (Paris). 177, 536–543. https://doi.org/10.1016/j.neurol.2021.03.001.
Cristofol, R., Porquet, D., Corpas, R., Coto-Montes, A., Serret, J., Camins, A., Pallas, M., Sanfeliu, C., 2012. Neurons from senescence-accelerated SAMP8 mice are protected against frailty by the sirtuin 1 promoting agents melatonin and resveratrol. J. Pineal Res. 52, 271–281. https://doi.org/10.1111/j.1600-079X.2011.00939.x.
Csiszar, A., Ungvari, A., Patai, R., Gulej, R., Yabluchanskiy, A., Benyo, Z., Kovacs, I., Sotonyi, P., Kirkpartrick, A.C., Prodan, C.I., Liotta, E.M., Zhang, X.A., Toth, P., Tarantini, S., Sorond, F.A., Ungvari, Z., 2024. Atherosclerotic burden and cerebral small vessel disease: exploring the link through microvascular aging and cerebral microhemorrhages. Geroscience. https://doi.org/10.1007/s11357-024-01139-7.
Cucielo, M.S., Freire, P.P., Emilio-Silva, M.T., Romagnoli, G.G., Carvalho, R.F., Kaneno, R., Hiruma-Lima, C.A., Delella, F.K., Reiter, R.J., Chuffa, L.G.A., 2023. Melatonin enhances cell death and suppresses the metastatic capacity of ovarian cancer cells by attenuating the signaling of multiple kinases. Pathol. Res. Pract. 248, 154637 https://doi.org/10.1016/j.prp.2023.154637.
Dai, E., Wang, W., Li, Y., Ye, D., Li, Y., 2024. Lactate and lactylation: behind the development of tumors. Cancer Lett. 591, 216896 https://doi.org/10.1016/j.canlet.2024.216896.
de Almeida Chuffa, L.G., Seiva, F.R.F., Silveira, H.S., Cesario, R.C., da Silva Tonon, K., Simao, V.A., Zuccari, D., Reiter, R.J., 2024. Melatonin regulates endoplasmic reticulum stress in diverse pathophysiological contexts: a comprehensive mechanistic review. J. Cell. Physiol., e31383 https://doi.org/10.1002/jcp.31383.
Devi, L., Prabhu, B.M., Galati, D.F., Avadhani, N.G., Anandatheerthavarada, H.K., 2006. Accumulation of amyloid precursor protein in the mitochondrial import channels of human Alzheimer's disease brain is associated with mitochondrial dysfunction. J. Neurosci. 26, 9057–9068. https://doi.org/10.1523/JNEUROSCI.1469-06.2006.
Diaz-Casado, M.E., Lima, E., Garcia, J.A., Doerrier, C., Aranda, P., Sayed, R.K., Guerra-Librero, A., Escames, G., Lopez, L.C., Acuna-Castroviejo, D., 2016. Melatonin rescues zebrafish embryos from the parkinsonian phenotype restoring the parkin/PINK1/DJ-1/MUL1 network. J. Pineal Res 61, 96–107. https://doi.org/10.1111/jpi.12332.
Domhan, S., Ma, L., Tai, A., Anaya, Z., Beheshti, A., Zeier, M., Hlatky, L., Abdollahi, A., 2011. Intercellular communication by exchange of cytoplasmic material via tunneling nano-tube like structures in primary human renal epithelial cells. PLoS One 6, e21283. https://doi.org/10.1371/journal.pone.0021283.
Dragicevic, N., Copes, N., O'Neal-Moffitt, G., Jin, J., Buzzeo, R., Mamcarz, M., Tan, J., Cao, C., Olcese, J.M., Arendash, G.W., Bradshaw, P.C., 2011. Melatonin treatment restores mitochondrial function in Alzheimer's mice: a mitochondrial protective role of melatonin membrane receptor signaling. J. Pineal Res. 51, 75–86. https://doi.org/10.1111/j.1600-079X.2011.00864.x.
Erren, T.C., Reiter, R.J., 2009. Defining chronodisruption. J. Pineal Res 46, 245–247. https://doi.org/10.1111/j.1600-079X.2009.00665.x.
Feng, Y., Jiang, X., Liu, W., Lu, H., 2023. The location, physiology, pathology of hippocampus Melatonin MT(2) receptor and MT(2)-selective modulators. Eur. J. Med. Chem. 262, 115888 https://doi.org/10.1016/j.ejmech.2023.115888.
Ferreira-Vieira, T.H., Guimaraes, I.M., Silva, F.R., Ribeiro, F.M., 2016. Alzheimer's disease: targeting the cholinergic system. Curr. Neuropharmacol. 14, 101–115. https://doi.org/10.2174/1570159x13666150716165726.
Gaiotte, L.B., Cesário, R.C., Silveira, H.S., de Morais Oliveira, D.A., Cucielo, M.S., Romagnoli, G.G., Kaneno, R., de Campos Zuccari, D.A.P., Reiter, R.J., Chuffa, L.G.A., 2022. Combination of melatonin with paclitaxel reduces the TLR4-mediated inflammatory pathway, PD-L1 levels, and survival of ovarian carcinoma cells. Melatonin Res 5, 34–51. https://doi.org/10.32794/mr112500118.
Galano, A., Medina, M.E., Tan, D.X., Reiter, R.J., 2015. Melatonin and its metabolites as copper chelating agents and their role in inhibiting oxidative stress: a physicochemical analysis. J. Pineal Res. 58, 107–116. https://doi.org/10.1111/jpi.12196.
Galano, A., Reiter, R.J., 2018. Melatonin and its metabolites vs oxidative stress: From individual actions to collective protection. J. Pineal Res. 65, e12514 https://doi.org/10.1111/jpi.12514.
Galano, A., Tan, D.X., Reiter, R.J., 2018. Melatonin: a versatile protector against oxidative DNA damage. Molecules 23. https://doi.org/10.3390/molecules23030530.
Garcia, S., Martin Gimenez, V.M., Mocayar Maron, F.J., Reiter, R.J., Manucha, W., 2020. Melatonin and cannabinoids: mitochondrial-targeted molecules that may reduce inflammaging in neurodegenerative diseases. Histol. Histopathol. 35, 789–800. https://doi.org/10.14670/HH-18-212.
Giri, A., Mehan, S., Khan, Z., Das Gupta, G., Narula, A.S., Kalfin, R., 2024. Modulation of neural circuits by melatonin in neurodegenerative and neuropsychiatric disorders.

Naunyn Schmiede Arch. Pharmacol. 397, 3867–3895. https://doi.org/10.1007/s00210-023-02939-y.
Glatfelter, G.C., Jones, A.J., Rajnarayanan, R.V., Dubocovich, M.L., 2021. Pharmacological actions of carbamate insecticides at mammalian melatonin receptors. J. Pharm. Exp. Ther. 376, 306–321. https://doi.org/10.1124/jpet.120.000065.
Gow, A., Sharma, R., 2003. The unfolded protein response in protein aggregating diseases. Neuromol. Med. 4, 73–94. https://doi.org/10.1385/NMM:4:1-2:73.
Grimm, A., Friedland, K., Eckert, A., 2016. Mitochondrial dysfunction: the missing link between aging and sporadic Alzheimer's disease. Biogerontology 17, 281–296. https://doi.org/10.1007/s10522-015-9618-4.
Grimm, A., Eckert, A., 2017. Brain aging and neurodegeneration: from a mitochondrial point of view. J. Neurochem. 143, 418–431. https://doi.org/10.1111/jnc.14037.
Gu, C., Zhou, Q., Hu, X., Ge, X., Hou, M., Wang, W., Liu, H., Shi, Q., Xu, Y., Zhu, X., Yang, H., Chen, X., Liu, T., He, F., 2024. Melatonin rescues the mitochondrial function of bone marrow-derived mesenchymal stem cells and improves the repair of osteoporotic bone defect in ovariectomized rats. J. Pineal Res. 76, e12924 https://doi.org/10.1111/jpi.12924.
Gu, Q., Wang, C., Xiao, Q., Chen, Z., Han, Y., 2021. Melatonin confers plant cadmium tolerance: an update. Int. J. Mol. Sci. 22, 11704. https://doi.org/10.3390/ijms222111704.
Halliwell, B., Adhikary, A., Dingfelder, M., Dizdaroglu, M., 2021. Hydroxyl radical is a significant player in oxidative DNA damage in vivo. Chem. Soc. Rev. 50, 8355–8360. https://doi.org/10.1039/d1cs00044f.
Hardeland, R., Tan, D.X., Reiter, R.J., 2009. Kynuramines, metabolites of melatonin and other indoles: the resurrection of an almost forgotten class of biogenic amines. J. Pineal Res. 47, 109–126. https://doi.org/10.1111/j.1600-079X.2009.00701.x.
Hardeland, R., 2019. Aging, melatonin, and the pro- and anti-inflammatory networks. Int. J. Mol. Sci. 20, 1223. https://doi.org/10.3390/ijms20051223.
Hardeland, R., 2022. Redox biology of melatonin: discriminating between circadian and noncircadian functions. Antioxid. Redox Signal. 37, 704–725. https://doi.org/10.1089/ars.2021.0275.
Hasan, M.K., Liu, C.X., Pan, Y.T., Ahammed, G.J., Qi, Z.Y., Zhou, J., 2018. Melatonin alleviates low-sulfur stress by promoting sulfur homeostasis in tomato plants. Sci. Rep. 8, 10182 https://doi.org/10.1038/s41598-018-28561-0.
Hautke, A., Ebbinghaus, S., 2023. The emerging role of ATP as a cosolute for biomolecular processes. Biol. Chem. 404, 897–908. https://doi.org/10.1515/hsz-2023-0202.
Hayakawa, K., Esposito, E., Wang, X., Terasaki, Y., Liu, Y., Xing, C., Ji, X., Lo, E.H., 2016. Transfer of mitochondria from astrocytes to neurons after stroke. Nature 535, 551–555. https://doi.org/10.1038/nature18928.
He, C., Wang, J., Zhang, Z., Yang, M., Li, Y., Tian, X., Ma, T., Tao, J., Zhu, K., Song, Y., Ji, P., Liu, G., 2016. Mitochondria synthesize melatonin to ameliorate its function and improve mice oocyte's quality under in vitro conditions. Int. J. Mol. Sci. 17, 939. https://doi.org/10.3390/ijms17060939.
He, W., Li, Q., Li, X., 2023. Acetyl-CoA regulates lipid metabolism and histone acetylation modification in cancer. Biochim Biophys. Acta Rev. Cancer 1878, 188837. https://doi.org/10.1016/j.bbcan.2022.188837.
Hedlund, L., Lischko, M.M., Rollag, M.D., Niswender, G.D., 1977. Melatonin: daily cycle in plasma and cerebrospinal fluid of calves. Science 195, 686–687. https://doi.org/10.1126/science.841305.
Hertz, H., Carstensen, M.B., Bering, T., Rohde, K., Moller, M., Granau, A.M., Coon, S.L., Klein, D.C., Rath, M.F., 2020. The Lhx4 homeobox transcript in the rat pineal gland: Adrenergic regulation and impact on transcripts encoding melatonin-synthesizing enzymes. J. Pineal Res. 68, e12616 https://doi.org/10.1111/jpi.12616.
Huether, G., 1993. The contribution of extrapineal sites of melatonin synthesis to circulating melatonin levels in higher vertebrates. Experientia 49, 665–670. https://doi.org/10.1007/BF01923948.
Huo, X., Wang, C., Yu, Z., Peng, Y., Wang, S., Feng, S., Zhang, S., Tian, X., Sun, C., Liu, K., Deng, S., Ma, X., 2017. Human transporters, PEPT1/2, facilitate melatonin transportation into mitochondria of cancer cells: an implication of the therapeutic potential. J. Pineal Res. 62, e12390 https://doi.org/10.1111/jpi.12390.
Ikari, N., Honjo, K., Sagami, Y., Nakamura, Y., Arakawa, H., 2024. Mieap forms membrane-less organelles involved in cardiolipin metabolism. iScience 27, 108916. https://doi.org/10.1016/j.isci.2024.108916.
Iwashita, H., Matsumoto, Y., Maruyama, Y., Watanabe, K., Chiba, A., Hattori, A., 2021. The melatonin metabolite N1-acetyl-5-methoxykynuramine facilitates long-term object memory in young and aging mice. J. Pineal Res. 70, e12703 https://doi.org/10.1111/jpi.12703.
Jauhari, A., Baranov, S.V., Suofu, Y., Kim, J., Singh, T., Yablonska, S., Li, F., Wang, X., Oberly, P., Minnigh, M.B., Poloyac, S.M., Carlisle, D.L., Friedlander, R.M., 2020. Melatonin inhibits cytosolic mitochondrial DNA-induced neuroinflammatory signaling in accelerated aging and neurodegeneration. J. Clin. Invest. 130, 3124–3136. https://doi.org/10.1172/JCI135026.
Jenwitheesuk, A., Park, S., Wongchitrat, P., Tocharus, J., Mukda, S., Shimokawa, I., Govitrapong, P., 2018. Comparing the effects of melatonin with caloric restriction in the hippocampus of aging mice: involvement of sirtuin1 and the FOXOs pathway. Neurochem. Res. 43, 153–161. https://doi.org/10.1007/s11064-017-2369-7.
Jezek, P., Dlaskova, A., Engstova, H., Spackova, J., Tauber, J., Pruchova, P., Kloppel, E., Mozheitova, O., Jaburek, M., 2024. Mitochondrial physiology of cellular redox regulations. Physiol. Res.
Jiao, L., Hu, C.X., Zhang, Y., Zhang, Y.X., Cai, W.W., Pan, W.L., Sun, S.C., Zhang, Y., 2023. SIRT3 regulates levels of deacetylated SOD2 to prevent oxidative stress and mitochondrial dysfunction during oocyte maturation in pigs. Microsc. Microanal. 29, 2149–2160. https://doi.org/10.1093/micmic/ozad127.
Jomova, K., Alomar, S.Y., Alwasel, S.H., Nepovimova, E., Kuca, K., Valko, M., 2024. Several lines of antioxidant defense against oxidative stress: antioxidant enzymes, nanomaterials with multiple enzyme-mimicking activities, and low-molecular-weight antioxidants. Arch. Toxicol. 98, 1323–1367. https://doi.org/10.1007/s00204-024-03696-4.
Joseph, T.T., Schuch, V., Hossack, D.J., Chakraborty, R., Johnson, E.L., 2024. Melatonin: the placental antioxidant and anti-inflammatory. Front. Immunol. 15, 1339304 https://doi.org/10.3389/fimmu.2024.1339304.
Jou, M.J., Peng, T.I., Reiter, R.J., 2019. Protective stabilization of mitochondrial permeability transition and mitochondrial oxidation during mitochondrial Ca(2+) stress by melatonin's cascade metabolites C3-OHM and AFMK in RBA1 astrocytes. J. Pineal Res. 66, e12538 https://doi.org/10.1111/jpi.12538.
Kakafika, M.G., Lyta, A.A., Gavriilidis, G.I., Tsiftsoglou, S.A., Miliotou, A.N., Pappas, I.S., Vizirianakis, I.S., Papadopoulou, L.C., Tsiftsoglou, A.S., 2024. Targeting mitochondrial bioenergetics by combination treatment with imatinib and dichloroacetate in human erythroleukemic K-562 and colorectal HCT-116 cancer cells. Int. J. Oncol. 64, 42. https://doi.org/10.3892/ijo.2024.5630.
Kanematsu, N., Mori, Y., Hayashi, S., Hoshino, K., 1989. Presence of a distinct 24-hour melatonin rhythm in the ventricular cerebrospinal fluid of the goat. J. Pineal Res. 7, 143–152. https://doi.org/10.1111/j.1600-079x.1989.tb00662.x.
Kerenyi, N.A., Balogh, I., Somogyi, E., Sotonyi, P., 1979. Cytochemical investigation of acetyl-serotonin-transferase activity in the pineal gland. Cell. Mol. Biol. Incl. Cyto Enzymol. 25, 259–262.
Kim, J., Li, W., Wang, J., Baranov, S.V., Heath, B.E., Jia, J., Suofu, Y., Baranova, O.V., Wang, X., Larkin, T.M., Lariviere, W.R., Carlisle, D.L., Friedlander, R.M., 2023. Biosynthesis of neuroprotective melatonin is dysregulated in Huntington's disease. J. Pineal Res. 75, e12909 https://doi.org/10.1111/jpi.12909.
Klein, D.C., 2007. Arylalkylamine N-acetyltransferase: "the Timezyme. J. Biol. Chem. 282, 4233–4237. https://doi.org/10.1074/jbc.R600036200.
Klimova, N., Long, A., Scafidi, S., Kristian, T., 2019. Interplay between NAD(+) and acetyl-CoA metabolism in ischemia-induced mitochondrial pathophysiology. Biochim Biophys. Acta Mol. Basis Dis. 1865, 2060–2067. https://doi.org/10.1016/j.bbadis.2018.09.025.
Klosen, P., 2024. Thirty-seven years of MT1 and MT2 melatonin receptor localization in the brain: past and future challenges. J. Pineal Res. 76, e12955 https://doi.org/10.1111/jpi.12955.
Kumar, V., Maity, S., 2021. ER stress-sensor proteins and ER-mitochondrial crosstalk-signaling beyond (ER) stress response. Biomolecules 11, 173. https://doi.org/10.3390/biom11020173.
Kuramochi, M., Nakamura, M., Takahashi, H., Komoriya, T., Takita, T., Pham, N.T.K., Yasukawa, K., Yoshimune, K., 2024. Adenosine triphosphate induces amorphous aggregation of amyloid beta by increasing Abeta dynamics. Sci. Rep. 14, 8134. https://doi.org/10.1038/s41598-024-58773-6.
Kvetnoy, I., Sandvik, A.K., Waldum, H.L., 1997. The diffuse neuroendocrine system and extrapineal melatonin. J. Mol. Endocrinol. 18, 1–3. https://doi.org/10.1677/jme.0.0180001.
Lee, H., Yoon, Y., 2016. Mitochondrial fission and fusion. Biochem. Soc. Trans. 44, 1725–1735. https://doi.org/10.1042/BST20160129.
Lee, L.E., Doke, T., Mukhi, D., Susztak, K., 2024a. The key role of altered tubule cell lipid metabolism in kidney disease development. Kidney Int. https://doi.org/10.1016/j.kint.2024.02.025.
Lee, M.J., Saner, N.J., Ferri, A., Garcia-Dominguez, E., Broatch, J.R., Bishop, D.J., 2024b. Delineating the contribution of ageing and physical activity to changes in mitochondrial characteristics across the lifespan. Mol. Asp. Med. 97, 101272 https://doi.org/10.1016/j.mam.2024.101272.
Legros, C., Chesneau, D., Boutin, J.A., Barc, C., Malpaux, B., 2014. Melatonin from cerebrospinal fluid but not from blood reaches sheep cerebral tissues under physiological conditions. J. Neuroendocrinol. 26, 151–163. https://doi.org/10.1111/jne.12134.
Lei, X., Xu, Z., Huang, L., Huang, Y., Tu, S., Xu, L., Liu, D., 2023. The potential influence of melatonin on mitochondrial quality control: a review. Front. Pharmacol. 14, 1332567 https://doi.org/10.3389/fphar.2023.1332567.
Leston, J., Harthe, C., Mottolese, C., Mertens, P., Sindou, M., Claustrat, B., 2015. Is pineal melatonin released in the third ventricle in humans? A study in movement disorders. Neurochirurgie 61, 85–89. https://doi.org/10.1016/j.neuchi.2013.04.004.
Lewis Lujan, L.M., McCarty, M.F., Di Nicolantonio, J.J., Galvez Ruiz, J.C., Rosas-Burgos, E.C., Plascencia-Jatomea, M., Iloki Assanga, S.B., 2022. Nutraceuticals/drugs promoting mitophagy and mitochondrial biogenesis may combat the mitochondrial dysfunction driving progression of dry age-related macular degeneration. Nutrients 14. https://doi.org/10.3390/nu14091985.
Li, B., Xiao, X., Bi, M., Jiao, Q., Chen, X., Yan, C., Du, X., Jiang, H., 2024a. Modulating alpha-synuclein propagation and decomposition: Implications in Parkinson's disease therapy. Ageing Res Rev. 98, 102319 https://doi.org/10.1016/j.arr.2024.102319.
Li, M., Hao, B., Zhang, M., Reiter, R.J., Lin, S., Zheng, T., Chen, X., Ren, Y., Yue, L., Abay, B., Chen, G., Xu, X., Shi, Y., Fan, L., 2021. Melatonin enhances radiofrequency-induced NK antitumor immunity, causing cancer metabolism reprogramming and inhibition of multiple pulmonary tumor development. Signal Transduct. Target Ther. 6, 330. https://doi.org/10.1038/s41392-021-00745-7.
Li, Y., Yu, H., Xu, Z., Shi, S., Wang, D., Shi, X., Wang, Y., Zeng, B., Deng, H., Deng, X., Zhong, X., 2019. Melatonin ameliorates ANIT-induced cholestasis by activating Nrf2 through a PI3K/Akt-dependent pathway in rats. Mol. Med Rep. 19, 1185–1193. https://doi.org/10.3892/mmr.2018.9746.
Li, Y., Tan, Y., Zhao, Z., 2024b. Impacts of aging on circadian rhythm and related sleep disorders. Biosystems 236, 105111. https://doi.org/10.1016/j.biosystems.2023.105111.

Limson, J., Nyokong, T., Daya, S., 1998. The interaction of melatonin and its precursors with aluminium, cadmium, copper, iron, lead, and zinc: an adsorptive voltammetric study. J. Pineal Res. 24, 15–21. https://doi.org/10.1111/j.1600-079x.1998.tb00361.x.

Linsenmeier, M., Faltova, L., Morelli, C., Capasso Palmiero, U., Seiffert, C., Kuffner, A.M., Pinotsi, D., Zhou, J., Mezzenga, R., Arosio, P., 2023. The interface of condensates of the hnRNPA1 low-complexity domain promotes formation of amyloid fibrils. Nat. Chem. 15, 1340–1349. https://doi.org/10.1038/s41557-023-01289-9.

Liu, Y., Fu, T., Li, G., Li, B., Luo, G., Li, N., Geng, Q., 2023. Mitochondrial transfer between cell crosstalk - an emerging role in mitochondrial quality control. Ageing Res Rev. 91, 102038 https://doi.org/10.1016/j.arr.2023.102038.

Loh, D., Reiter, R.J., 2021. Melatonin: Regulation of Biomolecular Condensates in Neurodegenerative Disorders. Antioxidants 10, 1483. https://doi.org/10.3390/antiox10091483.

Loh, D., Reiter, R., 2024. Melatonin, ATP, and cataracts: the two faces of crystallin phase separation. Qeios 48.

Luchetti, F., Carloni, S., Nasoni, M.G., Reiter, R.J., Balduini, W., 2023. Melatonin, tunneling nanotubes, mesenchymal cells, and tissue regeneration. Neural Regen. Res 18, 760–762. https://doi.org/10.4103/1673-5374.353480.

Lygate, C.A., 2024. Maintaining energy provision in the heart: the creatine kinase system in ischaemia-reperfusion injury and chronic heart failure. Clin. Sci. (Lond.). 138, 491–514. https://doi.org/10.1042/CS20230616.

Maffeis, V., Skowicki, M., Wolf, K.M.P., Chami, M., Schoenenberger, C.A., Vogel, V., Palivan, C.G., 2024. Advancing the design of artificial nano-organelles for targeted cellular detoxification of reactive oxygen species. Nano Lett. 24, 2698–2704. https://doi.org/10.1021/acs.nanolett.3c03888.

Majid, A., Garg, S., 2024. Reactive oxygen species may cause amyloid beta aggregation by free radical polymerization. J. Appl. Polym. Sci. 141, e55190 https://doi.org/10.1002/app.55190.

Manchester, L.C., Poeggeler, B., Alvares, F.L., Ogden, G.B., Reiter, R.J., 1995. Melatonin immunoreactivity in the photosynthetic prokaryote Rhodospirillum rubrum: implications for an ancient antioxidant system. Cell Mol. Biol. Res 41, 391–395.

Mao, L., Dauchy, R.T., Blask, D.E., Dauchy, E.M., Slakey, L.M., Brimer, S., Yuan, L., Xiang, S., Hauch, A., Smith, K., Frasch, T., Belancio, V.P., Wren, M.A., Hill, S.M., 2016. Melatonin suppression of aerobic glycolysis (Warburg effect), survival signalling and metastasis in human leiomyosarcoma. J. Pineal Res. 60, 167–177. https://doi.org/10.1111/jpi.12298.

Markus, R.P., Sousa, K.S., da Silveira Cruz-Machado, S., Fernandes, P.A., Ferreira, Z.S., 2021. Possible role of pineal and extra-pineal melatonin in surveillance, immunity, and first-line defense. Int. J. Mol. Sci. 22, 12143. https://doi.org/10.3390/ijms222212143.

Martin Gimenez, V.M., de Las Heras, N., Lahera, V., Tresguerres, J.A.F., Reiter, R.J., Manucha, W., 2022. Melatonin as an anti-aging therapy for age-related cardiovascular and neurodegenerative diseases. Front. Aging Neurosci. 14, 888292 https://doi.org/10.3389/fnagi.2022.888292.

Maurizi, C.P., 1991. Recirculation of cerebrospinal fluid through the tela choroidae is why high levels of melatonin can be found in the lateral ventricles. Med. Hypotheses 35, 154–158. https://doi.org/10.1016/0306-9877(91)90041-v.

Mayo, J.C., Aguado, A., Cernuda-Cernuda, R., Alvarez-Artime, A., Cepas, V., Quiros-Gonzalez, I., Hevia, D., Sainz, R.M., 2018. Melatonin Uptake by Cells: An Answer to Its Relationship with Glucose? Molecules 23. https://doi.org/10.3390/molecules23081999.

Mead, R.J., Shan, N., Reiser, H.J., Marshall, F., Shaw, P.J., 2023. Amyotrophic lateral sclerosis: a neurodegenerative disorder poised for successful therapeutic translation. Nat. Rev. Drug Discov. 22, 185–212. https://doi.org/10.1038/s41573-022-00612-2.

Megha, K.B., Arathi, A., Shikha, S., Alka, R., Ramya, P., Mohanan, P.V., 2024. Significance of melatonin in the regulation of circadian rhythms and disease management. Mol. Neurobiol. https://doi.org/10.1007/s12035-024-03915-0.

Moiseenok, A.G., Kanunnikova, N.P., 2023. Brain CoA and acetyl coa metabolism in mechanisms of neurodegeneration. Biochem. (Mosc. 88, 466–480. https://doi.org/10.1134/S000629792304003X.

Mota, Ad.L., Jardim-Perassi, B.V., Castro, T.B., Colombo, J., Sonehara, N.M., Nishiyama, V.K.G., Pierri, V.A.G., Zuccari, D.A.Pd.C., 2019. Melatonin modifies tumor hypoxia and metabolism by inhibiting HIF-1α and energy metabolic pathway in the in vitro and in vivo models of breast cancer. Melatonin Res 2, 83–98. https://doi.org/10.32794/mr11250042.

Munro, D., Pamenter, M.E., 2019. Comparative studies of mitochondrial reactive oxygen species in animal longevity: technical pitfalls and possibilities. Aging Cell 18, e13009. https://doi.org/10.1111/acel.13009.

Nakahira, K., Haspel, J.A., Rathinam, V.A., Lee, S.J., Dolinay, T., Lam, H.C., Englert, J.A., Rabinovitch, M., Cernadas, M., Kim, H.P., Fitzgerald, K.A., Ryter, S.W., Choi, A.M., 2011. Autophagy proteins regulate innate immune responses by inhibiting the release of mitochondrial DNA mediated by the NALP3 inflammasome. Nat. Immunol. 12, 222–230. https://doi.org/10.1038/ni.1980.

Nasoni, M.G., Carloni, S., Canonico, B., Burattini, S., Cesarini, E., Papa, S., Pagliarini, M., Ambrogini, P., Balduini, W., Luchetti, F., 2021. Melatonin reshapes the mitochondrial network and promotes intercellular mitochondrial transfer via tunneling nanotubes after ischemic-like injury in hippocampal HT22 cells. J. Pineal Res. 71, e12747 https://doi.org/10.1111/jpi.12747.

Nikolenko, V.N., Borminskaya, I.D., Nikitina, A.T., Golyshkina, M.S., Rizaeva, N.A., Oganesyan, M.V., 2024. Locus coeruleus-norepinephrine system: spheres of influence and contribution to the development of neurodegenerative diseases. Front Biosci. (Landmark Ed. 29, 118. https://doi.org/10.31083/j.fbl2903118.

Nopparat, C., Chaopae, W., Boontem, P., Sopha, P., Wongchitrat, P., Govitrapong, P., 2022. Melatonin attenuates high glucose-induced changes in beta amyloid precursor protein processing in human neuroblastoma cells. Neurochem. Res. 47, 2568–2579. https://doi.org/10.1007/s11064-021-03290-5.

Nous, A., Engelborghs, S., Smolders, I., 2021. Melatonin levels in the Alzheimer's disease continuum: a systematic review. Alzheimers Res. Ther. 13, 52. https://doi.org/10.1186/s13195-021-00788-6.

Novais, A.A., Chuffa, L.G.A., Zuccari, D., Reiter, R.J., 2021. Exosomes and melatonin: where their destinies intersect. Front. Immunol. 12, 692022 https://doi.org/10.3389/fimmu.2021.692022.

Novorolsky, R.J., Kasheke, G.D.S., Hakim, A., Foldvari, M., Dorighello, G.G., Sekler, I., Vuligonda, V., Sanders, M.E., Renden, R.B., Wilson, J.J., Robertson, G.S., 2023. Preserving and enhancing mitochondrial function after stroke to protect and repair the neurovascular unit: novel opportunities for nanoparticle-based drug delivery. Front. Cell. Neurosci. 17, 1226630 https://doi.org/10.3389/fncel.2023.1226630.

Okamoto, H.H., Cecon, E., Nureki, O., Rivara, S., Jockers, R., 2024. Melatonin receptor structure and signaling. J. Pineal Res. 76, e12952 https://doi.org/10.1111/jpi.12952.

Orlinska, K., Ramos, P., Komosinska-Vassev, K., Olczyk, K., Stojko, J., Rzepecka-Stojko, A., Kiselova-Kaneva, Y., Ivanova, D., Olczyk, P., Pilawa, B., 2024. Application of electron paramagnetic resonance spectroscopy to examine free radicals formed in indapamide and torasemide storage under UV irradiation and at the higher temperatures which appear under light exposition. J. Pharm. Biomed. Anal. 242, 116057 https://doi.org/10.1016/j.jpba.2024.116057.

Pacini, N., Borziani, F., 2016. Oncostatic-cytoprotective effect of melatonin and other bioactive molecules: a common target in mitochondrial respiration. Int. J. Mol. Sci. 17, 341. https://doi.org/10.3390/ijms17030341.

Panmanee, J., Charoensutthivarakul, S., Cheng, C.W., Promthep, K., Mukda, S., Prasertporn, T., Nopparat, C., Teerapo, K., Supcharoen, P., Petchyam, N., Chetsawang, B., Govitrapong, P., Phanchana, M., 2024. A complex interplay between melatonin and RORbeta: RORbeta is unlikely a putative receptor for melatonin as revealed by biophysical assays. Mol. Neurobiol. https://doi.org/10.1007/s12035-024-04395-y.

Park, J.H., Hayakawa, K., 2021. Extracellular mitochondria signals in CNS disorders. Front Cell Dev. Biol. 9, 642853 https://doi.org/10.3389/fcell.2021.642853.

Park, S., Barnes, R., Lin, Y., Jeon, B.J., Najafi, S., Delaney, K.T., Fredrickson, G.H., Shea, J.E., Hwang, D.S., Han, S., 2020. Dehydration entropy drives liquid-liquid phase separation by molecular crowding. Commun. Chem. 3, 83. https://doi.org/10.1038/s42004-020-0328-8.

Patki, G., Lau, Y.S., 2011. Melatonin protects against neurobehavioral and mitochondrial deficits in a chronic mouse model of Parkinson's disease. Pharm. Biochem Behav. 99, 704–711. https://doi.org/10.1016/j.pbb.2011.06.026.

Perez-Gonzalez, A., Galano, A., Alvarez-Idaboy, J.R., Tan, D.X., Reiter, R.J., 2017. Radical-trapping and preventive antioxidant effects of 2-hydroxymelatonin and 4-hydroxymelatonin: contributions to the melatonin protection against oxidative stress. Biochim Biophys. Acta Gen. Subj. 1861, 2206–2217. https://doi.org/10.1016/j.bbagen.2017.06.016.

Perez-Gonzalez, A., Castaneda-Arriaga, R., Alvarez-Idaboy, J.R., Reiter, R.J., Galano, A., 2019. Melatonin and its metabolites as chemical agents capable of directly repairing oxidized DNA. J. Pineal Res. 66, e12539 https://doi.org/10.1111/jpi.12539.

Pi, H., Xu, S., Reiter, R.J., Guo, P., Zhang, L., Li, Y., Li, M., Cao, Z., Tian, L., Xie, J., Zhang, R., He, M., Lu, Y., Liu, C., Duan, W., Yu, Z., Zhou, Z., 2015. SIRT3-SOD2-mROS-dependent autophagy in cadmium-induced hepatotoxicity and salvage by melatonin. Autophagy 11, 1037–1051. https://doi.org/10.1080/15548627.2015.1052208.

Picard, M., Ritchie, D., Wright, K.J., Romestaing, C., Thomas, M.M., Rowan, S.L., Taivassalo, T., Hepple, R.T., 2010. Mitochondrial functional impairment with aging is exaggerated in isolated mitochondria compared to permeabilized myofibers. Aging Cell 9, 1032–1046. https://doi.org/10.1111/j.1474-9726.2010.00628.x.

Pinato, L., da Silveira Cruz-Machado, S., Franco, D.G., Campos, L.M., Cecon, E., Fernandes, P.A., Bittencourt, J.C., Markus, R.P., 2015. Selective protection of the cerebellum against intracerebroventricular LPS is mediated by local melatonin synthesis. Brain Struct. Funct. 220, 827–840. https://doi.org/10.1007/s00429-013-0686-4.

Pourhanifeh, M.H., Hosseinzadeh, A., Koosha, F., Reiter, R.J., Mehrzadi, S., 2024. Therapeutic effects of melatonin in the regulation of ferroptosis: a review of current evidence. Curr. Drug Targets. https://doi.org/10.2174/0113894501284110240426074746.

Quintela, T., Goncalves, I., Silva, M., Duarte, A.C., Guedes, P., Andrade, K., Freitas, F., Talhada, D., Albuquerque, T., Tavares, S., Passarinha, L.A., Cipolla-Neto, J., Santos, C.R.A., 2018. Choroid plexus is an additional source of melatonin in the brain. J. Pineal Res. 65, e12528 https://doi.org/10.1111/jpi.12528.

Reiter, R.J., Korkmaz, A., Paredes, S.D., Manchester, L.C., Tan, D.X., 2008. Melatonin reduces oxidative/nitrosative stress due to drugs, toxins, metals, and herbicides. Neuro Endocrinol. Lett. 29, 609–613.

Reiter, R.J., Tan, D.X., Fuentes-Broto, L., 2010. Melatonin: a multitasking molecule. Prog. Brain Res. 181, 127–151. https://doi.org/10.1016/S0079-6123(08)81008-4.

Reiter, R.J., Tan, D.X., Kim, S.J., Cruz, M.H., 2014. Delivery of pineal melatonin to the brain and SCN: role of canaliculi, cerebrospinal fluid, tanycytes and Virchow-Robin perivascular spaces. Brain Struct. Funct. 219, 1873–1887. https://doi.org/10.1007/s00429-014-0719-7.

Reiter, R.J., Sharma, R., Ma, Q., Rosales-Corral, S.A., Acuña-Castroviejo, D., Escames, G., 2019. Inhibition of mitochondrial pyruvate dehydrogenase kinase: a proposed mechanism by which melatonin causes cancer cells to overcome cytosolic glycolysis, reduce tumor biomass and reverse insensitivity to chemotherapy. Melatonin Res 2, 105–119. https://doi.org/10.32794/mr11250033.

Reiter, R.J., Sharma, R., Ma, Q., Rorsales-Corral, S., de Almeida Chuffa, L.G., 2020. Melatonin inhibits Warburg-dependent cancer by redirecting glucose oxidation to

the mitochondria: a mechanistic hypothesis. Cell. Mol. Life Sci. 77, 2527–2542. https://doi.org/10.1007/s00018-019-03438-1.
Reiter, R.J., Sharma, R., Pires de Campos Zuccari, D.A., de Almeida Chuffa, L.G., Manucha, W., Rodriguez, C., 2021a. Melatonin synthesis in and uptake by mitochondria: implications for diseased cells with dysfunctional mitochondria. Future Med. Chem. 13, 335–339. https://doi.org/10.4155/fmc-2020-0326.
Reiter, R.J., Sharma, R., Rosales-Corral, S., 2021b. Anti-Warburg Effect of Melatonin: A Proposed Mechanism to Explain its Inhibition of Multiple Diseases. Int. J. Mol. Sci. 22, 764. https://doi.org/10.3390/ijms22020764.
Reiter, R.J., Sharma, R., Rosales-Corral, S., de Campos Zuccari, D.A.P., de Almeida Chuffa, L.G., 2022. Melatonin: a mitochondrial resident with a diverse skill set. Life Sci. 301, 120612 https://doi.org/10.1016/j.lfs.2022.120612.
Reiter, R.J., Sharma, R., Cucielo, M.S., Tan, D.X., Rosales-Corral, S., Gancitano, G., de Almeida Chuffa, L.G., 2023. Brain washing and neural health: role of age, sleep, and the cerebrospinal fluid melatonin rhythm. Cell. Mol. Life Sci. 80, 88. https://doi.org/10.1007/s00018-023-04736-5.
Reiter, R.J., Sharma, R., Tan, D.X., Chuffa, L.G.A., da Silva, D.G.H., Slominski, A.T., Steinbrink, K., Kleszczynski, K., 2024. Dual sources of melatonin and evidence for different primary functions. Front. Endocrinol. (Lausanne). 15, 1414463 https://doi.org/10.3389/fendo.2024.1414463.
Reppert, S.M., 1997. Melatonin receptors: molecular biology of a new family of G protein-coupled receptors. J. Biol. Rhythms 12, 528–531. https://doi.org/10.1177/074873049701200606.
Ressmeyer, A.R., Mayo, J.C., Zelosko, V., Sainz, R.M., Tan, D.X., Poeggeler, B., Antolin, I., Zsizsik, B.K., Reiter, R.J., Hardeland, R., 2003. Antioxidant properties of the melatonin metabolite N1-acetyl-5-methoxykynuramine (AMK): scavenging of free radicals and prevention of protein destruction. Redox Rep. 8, 205–213. https://doi.org/10.1179/135100003225002709.
Richards, S.L., Wilkins, K.A., Swarbreck, S.M., Anderson, A.A., Habib, N., Smith, A.G., McAinsh, M., Davies, J.M., 2015. The hydroxyl radical in plants: from seed to seed. J. Exp. Bot. 66, 37–46. https://doi.org/10.1093/jxb/eru398.
Rodrigues, A.C.C., de, M., Camargo, L.T.F., Francisco Lopes, Y., Sallum, L.O., Napolitano, H.B., Camargo, A.J., 2021. Aqueous solvation study of melatonin using ab initio molecular dynamics. J. Mol. Liq. 343, 117451 https://doi.org/10.1016/j.molliq.2021.117451.
Rosales-Corral, S., Acuna-Castroviejo, D., Tan, D.X., Lopez-Armas, G., Cruz-Ramos, J., Munoz, R., Melnikov, V.G., Manchester, L.C., Reiter, R.J., 2012a. Accumulation of exogenous amyloid-beta peptide in hippocampal mitochondria causes their dysfunction: a protective role for melatonin. Oxid. Med. Cell. Longev. 2012, 843649 https://doi.org/10.1155/2012/843649.
Rosales-Corral, S.A., Acuna-Castroviejo, D., Coto-Montes, A., Boga, J.A., Manchester, L. C., Fuentes-Broto, L., Korkmaz, A., Ma, S., Tan, D.X., Reiter, R.J., 2012b. Alzheimer's disease: pathological mechanisms and the beneficial role of melatonin. J. Pineal Res. 52, 167–202. https://doi.org/10.1111/j.1600-079X.2011.00937.x.
Rossi, S.P., Matzkin, M.E., Riviere, E., Martinez, G., Ponzio, R., Levalle, O., Terradas, C., Calandra, R.S., Frungieri, M.B., 2023. Melatonin improves oxidative state and lactate metabolism in rodent Sertoli cells. Mol. Cell Endocrinol. 576, 112034 https://doi.org/10.1016/j.mce.2023.112034.
Roy, T., Padhi, S., Mazumder, R., Majee, C., Das, S., Monika, M., Mishra, R., Kapoor, B., 2024. Alleviating neurodegenerative diseases associated with mitochondrial defects by therapeutic biomolecules. Curr. Top. Med. Chem. 24, 1377–1407. https://doi.org/10.2174/0115680266299148240329062647.
Sack, R.L., Lewy, A.J., Erb, D.L., Vollmer, W.M., Singer, C.M., 1986. Human melatonin production decreases with age. J. Pineal Res. 3, 379–388. https://doi.org/10.1111/j.1600-079x.1986.tb00760.x.
Sameni, S., Syed, A., Marsh, J.L., Digman, M.A., 2016. The phasor-FLIM fingerprints reveal shifts from OXPHOS to enhanced glycolysis in Huntington Disease. Sci. Rep. 6, 34755 https://doi.org/10.1038/srep34755.
Sawant, R., Paret, K., Petrillo, J., Koenig, A., Wolowacz, S., Ronquest, N., Rickards, H., 2024. Health state utility estimates for value assessments of novel treatments in Huntington's disease: a systematic literature review. Health Qual. Life Outcomes 22, 33. https://doi.org/10.1186/s12955-024-02242-1.
Scarian, E., Viola, C., Dragoni, F., Di Gerlando, R., Rizzo, B., Diamanti, L., Gagliardi, S., Bordoni, M., Pansarasa, O., 2024. New insights into oxidative stress and inflammatory response in neurodegenerative diseases. Int. J. Mol. Sci. 25, 2698. https://doi.org/10.3390/ijms25052698.
Scholtens, R.M., van Munster, B.C., van Kempen, M.F., de Rooij, S.E., 2016. Physiological melatonin levels in healthy older people: a systematic review. J. Psychosom. Res. 86, 20–27. https://doi.org/10.1016/j.jpsychores.2016.05.005.
Shabalina, I.G., Edgar, D., Gibanova, N., Kalinovich, A.V., Petrovic, N., Vyssokikh, M.Y., Cannon, B., Nedergaard, J., 2024. Enhanced ROS production in mitochondria from prematurely aging mtDNA mutator mice. Biochem. (Mosc. 89, 279–298. https://doi.org/10.1134/S0006297924020081.
Shen, K., Pender, C.L., Bar-Ziv, R., Zhang, H., Wickham, K., Willey, E., Durieux, J., Ahmad, Q., Dillin, A., 2022a. Mitochondria as cellular and organismal signaling hubs. Annu Rev. Cell Dev. Biol. 38, 179–218. https://doi.org/10.1146/annurev-cellbio-120420-015303.
Shen, S., Liao, Q., Wong, Y.K., Chen, X., Yang, C., Xu, C., Sun, J., Wang, J., 2022b. The role of melatonin in the treatment of type 2 diabetes mellitus and Alzheimer's disease. Int. J. Biol. Sci. 18, 983–994. https://doi.org/10.7150/ijbs.66871.
Shi, C., Zeng, J., Li, Z., Chen, Q., Hang, W., Xia, L., Wu, Y., Chen, J., Shi, A., 2018. Melatonin mitigates kainic acid-induced neuronal tau hyperphosphorylation and memory deficits through alleviating ER stress. Front. Mol. Neurosci. 11, 5. https://doi.org/10.3389/fnmol.2018.00005.
Shukla, M., Govitrapong, P., Boontem, P., Reiter, R.J., Satayavivad, J., 2017. Mechanisms of melatonin in alleviating Alzheimer's disease. Curr. Neuropharmacol. 15, 1010–1031. https://doi.org/10.2174/1570159X15666170313123454.
Sies, H., Berndt, C., Jones, D.P., 2017. Oxidativestress. Annu. Rev. Biochem. 86, 715–748. https://doi.org/10.1146/annurev-biochem-061516-045037.
Sies, H., Jones, D.P., 2020. Reactive oxygen species (ROS) as pleiotropic physiological signalling agents. Nat. Rev. Mol. Cell Biol. 21, 363–383. https://doi.org/10.1038/s41580-020-0230-3.
Sies, H., 2021. Oxidative eustress: On constant alert for redox homeostasis. Redox Biol. 41, 101867 https://doi.org/10.1016/j.redox.2021.101867.
Singh, K., Barsoum, S., Schilling, K.G., An, Y., Ferrucci, L., Benjamini, D., 2024. Neuronal microstructural changes in the human brain are associated with neurocognitive aging. Aging Cell, e14166. https://doi.org/10.1111/acel.14166.
Singrang, N., Nopparat, C., Panmanee, J., Govitrapong, P., 2024. Melatonin inhibits hypoxia-induced Alzheimer's disease pathogenesis by regulating the amyloidogenic pathway in human neuroblastoma cells. Int. J. Mol. Sci. 25 https://doi.org/10.3390/ijms25105225.
Skinner, D.C., Malpaux, B., 1999. High melatonin concentrations in third ventricular cerebrospinal fluid are not due to Galen vein blood recirculating through the choroid plexus. Endocrinology 140, 4399–4405. https://doi.org/10.1210/endo.140.10.7074.
Slominski, R.M., Reiter, R.J., Schlabritz-Loutsevitch, N., Ostrom, R.S., Slominski, A.T., 2012. Melatonin membrane receptors in peripheral tissues: distribution and functions. Mol. Cell Endocrinol. 351, 152–166. https://doi.org/10.1016/j.mce.2012.01.004.
Sun, C., Qiu, X., Wang, Y., Liu, J., Li, Q., Jiang, H., Li, S., Song, C., 2020. Long-term oral melatonin alleviates memory deficits, reduces amyloid-beta deposition associated with downregulation of BACE1 and mitophagy in APP/PS1 transgenic mice. Neurosci. Lett. 735, 135192 https://doi.org/10.1016/j.neulet.2020.135192.
Suofu, Y., Li, W., Jean-Alphonse, F.G., Jia, J., Khattar, N.K., Li, J., Baranov, S.V., Leronni, D., Mihalik, A.C., He, Y., Cecon, E., Wehbi, V.L., Kim, J., Heath, B.E., Baranova, O.V., Wang, X., Gable, M.J., Kretz, E.S., Di Benedetto, G., Lezon, T.R., Ferrando, L.M., Larkin, T.M., Sullivan, M., Yablonska, S., Wang, J., Minnigh, M.B., Guillaumet, G., Suzenet, F., Richardson, R.M., Poloyac, S.M., Stolz, D.B., Jockers, R., Witt-Enderby, P.A., Carlisle, D.L., Vilardaga, J.P., Friedlander, R.M., 2017. Dual role of mitochondria in producing melatonin and driving GPCR signaling to block cytochrome c release. Proc. Natl. Acad. Sci. U. S. A. 114, E7997–E8006. https://doi.org/10.1073/pnas.1705768114.
Talbot, N.C., Luther, P.M., Spillers, N.J., Ragland, A.R., Kidder, E.J., Kelkar, R.A., Varrassi, G., Ahmadzadeh, S., Shekoohi, S., Kaye, A.D., 2023. Neuroprotective potential of melatonin: evaluating therapeutic efficacy in Alzheimer's and Parkinson's diseases. Cureus 15, e50948. https://doi.org/10.7759/cureus.50948.
Tan, D.-X., Chen, L.D., Poeggeler, B., Manchester, L.C., Reiter, R.J., 1993. Melatonin: a potent, endogenous hydroxyl radical scavenger. Endocr. J. 1, 57–60.
Tan, D.X., Hardeland, R., Manchester, L.C., Poeggeler, B., Lopez-Burillo, S., Mayo, J.C., Sainz, R.M., Reiter, R.J., 2003. Mechanistic and comparative studies of melatonin and classic antioxidants in terms of their interactions with the ABTS cation radical. J. Pineal Res. 34, 249–259. https://doi.org/10.1034/j.1600-079x.2003.00037.x.
Tan, D.X., Manchester, L.C., Liu, X., Rosales-Corral, S.A., Acuna-Castroviejo, D., Reiter, R.J., 2013. Mitochondria and chloroplasts as the original sites of melatonin synthesis: a hypothesis related to melatonin's primary function and evolution in eukaryotes. J. Pineal Res. 54, 127–138. https://doi.org/10.1111/jpi.12026.
Tan, D.X., Hardeland, R., Manchester, L.C., Galano, A., Reiter, R.J., 2014. Cyclic-3-hydroxymelatonin (C3HOM), a potent antioxidant, scavenges free radicals and suppresses oxidative reactions. Curr. Med. Chem. 21, 1557–1565. https://doi.org/10.2174/09298673216613129113146.
Tan, D.X., Manchester, L.C., Esteban-Zubero, E., Zhou, Z., Reiter, R.J., 2015. Melatonin as a potent and inducible endogenous antioxidant: synthesis and metabolism. Molecules 20, 18886–18906. https://doi.org/10.3390/molecules201018886.
Tauber, S.C., Nau, R., 2023. Treatment of septic encephalopathy and encephalitis - a critical appraisal. Expert Rev. Neurother. 23, 1069–1080. https://doi.org/10.1080/14737175.2023.2288652.
Thangwaritorn, S., Lee, C., Metchikoff, E., Razdan, V., Ghafary, S., Rivera, D., Pinto, A., Pemminati, S., 2024. A review of recent advances in the management of Alzheimer's disease. Cureus 16, e58416. https://doi.org/10.7759/cureus.58416.
Tozihi, M., Shademan, B., Yousefi, H., Avci, C.B., Nourazarian, A., Dehghan, G., 2023. Melatonin: a promising neuroprotective agent for cerebral ischemia-reperfusion injury. Front. Aging Neurosci. 15, 1227513 https://doi.org/10.3389/fnagi.2023.1227513.
Tricoire, H., Locatelli, A., Chemineau, P., Malpaux, B., 2002. Melatonin enters the cerebrospinal fluid through the pineal recess. Endocrinology 143, 84–90. https://doi.org/10.1210/endo.143.1.8585.
Tricoire, H., Moller, M., Chemineau, P., Malpaux, B., 2003. Origin of cerebrospinal fluid melatonin and possible function in the integration of photoperiod. Reprod. Suppl. 61, 311–321.
Vallee, A., Lecarpentier, Y., Guillevin, R., Vallee, J.N., 2018. Thermodynamics in neurodegenerative diseases: interplay between canonical WNT/beta-catenin pathway-PPAR gamma, energy metabolism and circadian rhythms. Neuromolecul. Med 20, 174–204. https://doi.org/10.1007/s12017-018-8486-x.
van Munster, M., Pedrosa, A.J., Kunkler, C., Pedrosa, D.J., 2024. The quality in quality of life in Parkinson's disease: a qualitative meta-synthesis. Mov. Disord. Clin. Pr. 9 https://doi.org/10.1002/mdc3.14063.
Venegas, C., Garcia, J.A., Escames, G., Ortiz, F., Lopez, A., Doerrier, C., Garcia-Corzo, L., Lopez, L.C., Reiter, R.J., Acuna-Castroviejo, D., 2012. Extrapineal melatonin: analysis of its subcellular distribution and daily fluctuations. J. Pineal Res. 52, 217–227. https://doi.org/10.1111/j.1600-079X.2011.00931.x.

Venegas, C., Garcia, J.A., Doerrier, C., Volt, H., Escames, G., Lopez, L.C., Reiter, R.J., Acuna-Castroviejo, D., 2013. Analysis of the daily changes of melatonin receptors in the rat liver. J. Pineal Res. 54, 313–321. https://doi.org/10.1111/jpi.12019.

Vriend, J., Reiter, R.J., 2015a. Melatonin feedback on clock genes: a theory involving the proteasome. J. Pineal Res. 58, 1–11. https://doi.org/10.1111/jpi.12189.

Vriend, J., Reiter, R.J., 2015b. The Keap1-Nrf2-antioxidant response element pathway: a review of its regulation by melatonin and the proteasome. Mol. Cell Endocrinol. 401, 213–220. https://doi.org/10.1016/j.mce.2014.12.013.

Wang, J., Gao, S., Lenahan, C., Gu, Y., Wang, X., Fang, Y., Xu, W., Wu, H., Pan, Y., Shao, A., Zhang, J., 2022. Melatonin as an antioxidant agent in stroke: an updated review. Aging Dis. 13, 1823–1844. https://doi.org/10.14336/AD.2022.0405.

Wang, P., Deng, J., Dong, J., Liu, J., Bigio, E.H., Mesulam, M., Wang, T., Sun, L., Wang, L., Lee, A.Y., McGee, W.A., Chen, X., Fushimi, K., Zhu, L., Wu, J.Y., 2019. TDP-43 induces mitochondrial damage and activates the mitochondrial unfolded protein response. PLoS Genet 15, e1007947. https://doi.org/10.1371/journal.pgen.1007947.

Wang, W., Zhao, F., Ma, X., Perry, G., Zhu, X., 2020. Mitochondria dysfunction in the pathogenesis of Alzheimer's disease: recent advances. Mol. Neurodegener. 15, 30. https://doi.org/10.1186/s13024-020-00376-6.

Wang, Y., Yang, H., Geerts, C., Furtos, A., Waters, P., Cyr, D., Wang, S., Mitchell, G.A., 2023. The multiple facets of acetyl-CoA metabolism: energetics, biosynthesis, regulation, acylation and inborn errors. Mol. Genet Metab. 138, 106966 https://doi.org/10.1016/j.ymgme.2022.106966.

Wongprayoon, P., Govitrapong, P., 2017. Melatonin as a mitochondrial protector in neurodegenerative diseases. Cell. Mol. Life Sci. 74, 3999–4014. https://doi.org/10.1007/s00018-017-2614-x.

Woolf, N.J., Butcher, L.L., 2011. Cholinergic systems mediate action from movement to higher consciousness. Behav. Brain Res. 221, 488–498. https://doi.org/10.1016/j.bbr.2009.12.046.

Wu, J., Yang, Y., Lin, D., Wang, Z., Ma, J., 2024. SIRT3 and RORalpha are two prospective targets against mitophagy during simulated ischemia/reperfusion injury in H9c2 cells. Heliyon 10, e30568. https://doi.org/10.1016/j.heliyon.2024.e30568.

Xia, A.Y., Zhu, H., Zhao, Z.J., Liu, H.Y., Wang, P.H., Ji, L.D., Xu, J., 2023. Molecular mechanisms of the melatonin receptor pathway linking circadian rhythm to type 2 diabetes mellitus. Nutrients 15, 1406. https://doi.org/10.3390/nu15061406.

Xie, H., Yu, Y., Yang, Y., Sun, Q., Li, Z.Y., Ni, M.H., Li, S.N., Dai, P., Cui, Y.Y., Cao, X.Y., Jiang, N., Du, L.J., Gao, W., Bi, J.J., Yan, L.F., Cui, G.B., 2023. Commonalities and distinctions between the type 2 diabetes mellitus and Alzheimer's disease: a systematic review and multimodal neuroimaging meta-analysis. Front. Neurosci. 17, 1301778 https://doi.org/10.3389/fnins.2023.1301778.

Xing, P.Y., Agrawal, R., Jayaraman, A., Martin, K.A., Zhang, G.W., Ngu, E.L., Faylon, L. E., Kjelleberg, S., Rice, S.A., Wang, Y., Bello, A.T., Holmes, E., Nicholson, J.K., Whiley, L., Pettersson, S., 2024. Microbial indoles: key regulators of organ growth and metabolic function. Microorganisms 12, 719. https://doi.org/10.3390/microorganisms12040719.

Yang, C., Pan, R.Y., Guan, F., Yuan, Z., 2024. Lactate metabolism in neurodegenerative diseases. Neural Regen. Res 19, 69–74. https://doi.org/10.4103/1673-5374.374142.

Yang, S.H., Li, W., Sumien, N., Forster, M., Simpkins, J.W., Liu, R., 2017. Alternative mitochondrial electron transfer for the treatment of neurodegenerative diseases and cancers: Methylene blue connects the dots. Prog. Neurobiol. 157, 273–291. https://doi.org/10.1016/j.pneurobio.2015.10.005.

Yip, H.K., Dubey, N.K., Lin, K.C., Sung, P.H., Chiang, J.Y., Chu, Y.C., Huang, C.R., Chen, Y.L., Deng, Y.H., Cheng, H.C., Deng, W.P., 2021. Melatonin rescues cerebral ischemic events through upregulated tunneling nanotube-mediated mitochondrial transfer and downregulated mitochondrial oxidative stress in rat brain. Biomed. Pharmacother. 139, 111593 https://doi.org/10.1016/j.biopha.2021.111593.

Yoo, Y.M., Joo, S.S., 2023. Melatonin can modulate neurodegenerative diseases by regulating endoplasmic reticulum stress. Int. J. Mol. Sci. 24 https://doi.org/10.3390/ijms24032381.

Zhang, C., Lin, M., Wu, R., Wang, X., Yang, B., Levine, A.J., Hu, W., Feng, Z., 2011. Parkin, a p53 target gene, mediates the role of p53 in glucose metabolism and the Warburg effect. Proc. Natl. Acad. Sci. U. S. A. 108, 16259–16264. https://doi.org/10.1073/pnas.1113884108.

Zhang, C., Ma, Y., Zhao, Y., Guo, N., Han, C., Wu, Q., Mu, C., Zhang, Y., Tan, S., Zhang, J., Liu, X., 2024a. Systematic review of melatonin in cerebral ischemia-reperfusion injury: critical role and therapeutic opportunities. Front. Pharmacol. 15, 1356112 https://doi.org/10.3389/fphar.2024.1356112.

Zhang, H., Shao, S., Zeng, Y., Wang, X., Qin, Y., Ren, Q., Xiang, S., Wang, Y., Xiao, J., Sun, Y., 2022. Reversible phase separation of HSF1 is required for an acute transcriptional response during heat shock. Nat. Cell Biol. 24, 340–352. https://doi.org/10.1038/s41556-022-00846-7.

Zhang, J., Feng, M., Kong, L., 2024b. The therapeutic potential of melatonin in Alzheimer's disease: a comprehensive review. Curr. Med. Chem. https://doi.org/10.2174/0109298673286807240326085736.

Zhang, Y., Cook, A., Kim, J., Baranov, S.V., Jiang, J., Smith, K., Cormier, K., Bennett, E., Browser, R.P., Day, A.L., Carlisle, D.L., Ferrante, R.J., Wang, X., Friedlander, R.M., 2013. Melatonin inhibits the caspase-1/cytochrome c/caspase-3 cell death pathway, inhibits MT1 receptor loss and delays disease progression in a mouse model of amyotrophic lateral sclerosis. Neurobiol. Dis. 55, 26–35. https://doi.org/10.1016/j.nbd.2013.03.008.

Zhao, D., Yu, Y., Shen, Y., Liu, Q., Zhao, Z., Sharma, R., Reiter, R.J., 2019. Melatonin synthesis and function: evolutionary history in animals and plants. Front. Endocrinol. (Lausanne). 10, 249. https://doi.org/10.3389/fendo.2019.00249.

Zheng, X., Tan, D.X., Allan, A.C., Zuo, B., Zhao, Y., Reiter, R.J., Wang, L., Wang, Z., Guo, Y., Zhou, J., Shan, D., Li, Q., Han, Z., Kong, J., 2017. Chloroplastic biosynthesis of melatonin and its involvement in protection of plants from salt stress. Sci. Rep. 7, 41236 https://doi.org/10.1038/srep41236.

Zhou, W., Yang, X., Wang, H., Yao, W., Chu, D., Wu, F., 2024. Neuronal aerobic glycolysis exacerbates synapse loss in aging mice. Exp. Neurol. 371, 114590 https://doi.org/10.1016/j.expneurol.2023.114590.

Zimmermann, A., Madeo, F., Diwan, A., Sadoshima, J., Sedej, S., Kroemer, G., Abdellatif, M., 2024. Metabolic control of mitophagy. Eur. J. Clin. Invest. 54, e14138 https://doi.org/10.1111/eci.14138.