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Chapter

Melatonin for a Healthy Heart Rhythm

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Abstract

Melatonin is a promising cardioprotective agent. Its increase during the night is associated with healthy cardiovascular function. On the other hand, reduced levels of melatonin are related to diseases. Aging and chronodisruptors reduce melatonin levels. Pharmacological supplementation reduces the deleterious effects of cardiovascular risk factors and improves the myocardial response to ischemia/reperfusion injury and other proarrhythmic conditions. The protective mechanisms of melatonin involve its antioxidant properties as well as receptor-mediated actions. Signaling pathways include membrane responses, cytoplasmic modulation of kinases, nuclear receptor interactions, and improvement of mitochondrial functions. This chapter focuses on the electrophysiological and the antiarrhythmic properties of melatonin. The acute and chronic protective mechanisms of melatonin will be analyzed with an emphasis on transmembrane potentials and intercellular communication. An outstanding antifibrillatory effect makes melatonin a novel antiarrhythmic agent worthy of further exploration in the path to clinical applications.

Keywords: melatonin, arrhythmias, ventricular fibrillation, action potential, connexin 43, melatonin receptors

1. Introduction

"Nothing to do to save his life…" says the Beatles song "Good morning, good morning." Ironically, cardiovascular mortality and life-threatening arrhythmias show a circadian increase in the mornings, and chronoprotective agents are still missing [1, 2]. This chapter highlights the importance of melatonin as a potential life-saving agent for the darkest nights (of antiarrhythmics drugs) and a brightest tomorrow.

The cardioprotective properties of melatonin are remarkable. Most of the preclinical and clinical studies support the protective actions and the safety profile of this indolamine [3, 4]. In this chapter, we briefly introduce the multitarget and versatile properties of melatonin and general concepts of electrophysiology to appreciate its potential as a promising antiarrhythmic agent. The second and third sections of the chapters focus on acute and chronic melatonin's antiarrhythmic effects.

1.1 Melatonin properties relevant to heart rhythms

Endogenous and pharmacological increases of melatonin concentrations protect the cardiovascular system [3–11]. However, the relationships between the cardiovascular and circadian systems are highly complex and should not be interpreted in reductionist ways [5, 12–14]. Furthermore, our understanding of the pleiotropy of melatonin, a highly preserved molecule of protection, is continuously expanding [3–7, 10, 15–24]. Therefore, we will focus on melatonin effects on heart rhythms. Additional information regarding melatonin cardiovascular effects can be found elsewhere and include direct actions in the heart, blood vessels, kidney, and other regulatory mechanisms at the nervous, immune, and endocrine systems [11, 25, 26]. Only the electrophysiological information will be extracted from its protective actions against risk factors like hypertension, metabolic syndrome, obesity, inflammation, and pathologies like ischemia/reperfusion injury, infarction, drug-induced cardiotoxicity, diabetic cardiomyopathy, and heart failure [8, 11, 21, 27].

Melatonin is amphipathic and pleiotropic. Melatonin can act on several targets at cell membranes and at intracellular levels in almost any cell [28, 29]. For this electrophysiological analysis, we present the following division of melatonin mechanisms of action:

a. Antioxidant

b. Receptor activation

c. Improvement of mitochondrial functions

d. Ion channel modulation

1.1.1 Melatonin as an antioxidant

Melatonin protects against oxidants by several mechanisms. In fact, it has been suggested that one of the main functions of melatonin in all living organisms is to protect them from oxidative stress [30, 31]. Melatonin has a well-characterized and extensively documented antioxidant capacity [31–37]. Melatonin is a powerful antioxidant, with a potency of up to 10 times greater than vitamin E [38].

There are oxidants of different chemical nature. They can be free radicals or non-radical reactive species [39, 40]. Free radicals—molecules with an unpaired electron—are unstable, highly reactive, and often trigger chain reactions, which propagate nearby molecular modifications. The most studied oxidants are the reactive oxygen species (ROS), reactive nitrogen species (RNS), and reactive sulfur species. Under physiological conditions, ROS/RNS act as second intracellular messengers modulating signal transduction pathways [40, 41]. A delicate cellular balance between the production and the removal of free radicals maintains low/moderate concentrations. Oxidative stress occurs when oxidants increase above healthy levels and represent a severe risk to the molecular integrity of lipids, proteins, and DNA [39, 40]. Therefore, neutralization of reactive species by scavenger molecules like melatonin is a chemical way of counteracting oxidative stress.

The main agent involved in oxidative damage is superoxide anion, but hydrogen peroxide, hydroxyl radical, nitric oxide (NO), peroxynitrite, and nitroxyl also participate in oxidative stress. The mitochondria are the main source of oxidizing species during oxidative phosphorylation. Oxidants are also the product of the activation of non-mitochondrial enzyme systems such as NADPH oxidase, xanthine oxidase, and nitric oxide synthase [40–42].

Cells have antioxidants that prevent damage. An antioxidant is any substance that significantly delays or prevents oxidation of lipids, proteins, or DNA [40]. Lipids are often used as target molecules because they are more reactive to oxidants than proteins or DNA. Nonenzymatic antioxidants include reduced glutathione (GSH), vitamins, and melatonin among others. Melatonin is five times more effective than GSH as scavenger of the highly toxic hydroxyl radical [34]. The main antioxidant enzymes are superoxide dismutase (SOD), catalase, thioredoxin, and glutathione peroxidase [40–44].

Melatonin efficiently prevents oxidative stress. The aromatic indole ring of melatonin reduces and repairs electrophilic radicals acting as generous electron donor. One molecule of melatonin can neutralize up to 10 toxic reagents, including ROS, RNS, and other free radicals [7, 39, 45–47]. In addition, several metabolites formed when melatonin neutralizes harmful reagents are also antioxidants suggesting that a cascade of reactions increases the efficacy of melatonin [28, 35, 47–49]. Being a highly lipophilic and hydrophilic compound, melatonin crosses all morphological barriers and acts not only in each cell but also within each subcellular compartment. Additionally, melatonin increases the efficacy of vitamin E, vitamin C, and GSH [33, 50]. Therefore, the elimination of free radicals can be carried out by intracellular interactions independent of any receptor [36, 45, 51].

Melatonin stimulates antioxidant enzymes by acting on membrane, cytoplasmic, and nuclear receptors [39, 43, 52]. Low melatonin concentrations increase the expression or activity of SOD, catalase, and glutathione peroxidase [43, 53].

Ion channels and many other proteins respond to oxidative stress [54–58]. Amino acid residues are the targets of ROS/RNS. Sulfur atoms like cysteine and methionine, hydroxyl groups from tyrosine, or aromatic rings of histidine, phenylalanine, and tryptophan are vulnerable to reactive species. Those that contain more cysteines are more sensitive to changes because thiol groups (–SH), which exist as thiolates (–S) at physiological pH, tend to react more quickly with ROS/RNS [59]. Many of these proteins are involved in important biological reactions such as oxidative phosphorylation, metabolic regulation, and signal transduction [60, 61]. Oxidative stress can increase late sodium currents through direct Na^+ channel modification [62, 63] and result in a prolonged action potential duration and arrhythmogenic triggers known as early-after depolarizations (EAD) [64]. Several reviews describe the redox regulation of calcium channel in cardiac myocytes including the ryanodine receptor calcium, the IP3 receptor, and voltage-dependent L-type calcium channel [65–69]. ROS and RNS affect the L-type Ca^{2+} channel Cav1.2 by regulation of cysteine residues. However, calcium channel regulation by redox is controversial with reports of increase and decrease of channel functions [66]. Voltage-gated potassium (Kv) channel, mainly responsible for myocardial repolarization, is sensitive to oxidative stress [58, 70–72]. Sulfenic acid modification at a conserved cysteine residue of Kv1.5 under prolonged oxidative stress can induce arrhythmia [58, 72].

1.1.2 Melatonin receptors

Melatonin has receptors in the cellular membranes, in the cytoplasm, and in the nucleus. Melatonin membrane receptors express in several regions of the nervous system and in almost all the organs including the heart, arteries, kidneys, liver, gastrointestinal tract, prostate gland, uterus, skin, and eyes [73]. Melatonin activates two subtypes of G-protein-coupled receptors in the plasma membrane, named MT1 and MT2, according to the official IUPHAR nomenclature (previously called Mel1a and Mel1b) [74]. Both receptors have high affinity to melatonin (K_d ~ 0.1 pM). In 2019, Stauch and Johansson reported the crystal structures of the human MT1 and MT2 and set a solid base concerning ligand recognition for both receptors [75, 76].

Melatonin membrane receptors can exist as monomers, as well as dimers. The MT1 homodimer forms 3- to 4-fold higher proportion than the MT2 homodimer and the MT1/MT2 heterodimer. Nonmammalian vertebrates present a third low-affinity receptor termed Mel1c, and a proposed mammalian homologous is the orphan receptor GPR50 [74, 77–79]. This orphan lost its properties to directly interact with melatonin but shows an inhibitory interaction with MT1 receptors by forming heterodimers. More recently, other orphans unable to bind melatonin like GPR61, GPR62, and GPR135 showed a similar indirect inhibitory interaction with MT2 receptors [80]. Other G-protein-coupled receptors like the serotonin receptor 5HT2c can interact with melatonin membrane receptors [79]. These interesting interactions of membrane receptors are not further discussed in this chapter but should be considered in future electrophysiological studies with melatonin.

The MT1 and MT2 inhibit adenylate cyclase-protein kinase A-CREB signaling in target cells by pertussis toxin-sensitive Gαi, β, and γ and toxin-insensitive Gq, β, and γ proteins [74, 79]. The MT1 also increases phosphorylation of mitogen-activated protein kinase 1/2 (MAPK) and extracellular signal-regulated kinase 1/2 (ERK), as well as increasing potassium conductance through inwardly rectifying (Kir3.x) channels. The later effect on potassium channels could be relevant to heart electrophysiology since Kir3.x channels are highly expressed in cardiomyocytes and usually coupled to acetylcholine and adenosine membrane receptors [81]. MT2 melatonin receptor activation inhibits both forskolin-stimulated cAMP production and cGMP formation, activates protein kinase C (PKC) in the nervous system, and decreases calcium-dependent dopamine release in the retina. Native functional MT1/MT2 heterodimers in mouse rod photoreceptors mediate melatonin's enhancement of scotopic light sensitivity through phospholipase C and PKC pathways [82].

Several compounds interact with MT1 and MT2 receptors, but blocker luzindole is the only with proven myocardial electrophysiological effects [83]. Luzindole and 4P-PDOT competitively block MT1 melatonin receptors at concentrations higher than 300 nM, and both are inverse agonists in systems with constitutively active MT1 receptors [74, 79].

Melatonin interacts with several enzymes and intracellular proteins. The MT3 receptors is a quinone reductase 2 with an affinity in the nanomolar ranges [84]. This enzyme is possibly involved in the regulation of cellular oxidative status, although the exact regulatory action of melatonin remains unclear [84–87]. Furthermore, the electrophysiological effects of MT3 have not been reported yet.

Melatonin interacts with intracellular proteins such as calmodulin, calreticulin, or tubulin [88]. The low-affinity interaction between melatonin and calmodulin antagonizes the binding of Ca^{2+} and may be involved in its antioxidant action as well as other electrophysiological signaling processes [89–96].

Melatonin increases the cytoplasmic levels of the heat shock protein 70 in several tissues including the heart [97–102]. Further interaction with this chaperon will be described in Section 3 of the chapter.

Melatonin is a ligand for the retinoid-related orphan nuclear hormone receptor family (RZR/ROR) [74, 79]. RZR/RORα is expressed in a variety of organs, whereas RZRβ is specific for the brain and retina [33]. ROR/RZR has been proposed to work in coordination with the plasma membrane receptors MT1/MT2 to regulate gene expression. We suggest a potential interaction with Vitamin D receptor (VDR), which was elegantly confirmed in recent experiments [97, 103].

1.1.3 Melatonin improves mitochondrial functions

Mitochondria are critical for cellular metabolism and energy production. They maintain life but also are gatekeepers of cell death [31, 104]. Mitochondria

produce up to 95% of the cellular energy in the form of ATP in aerobic cells [105]. Mitochondrial oxidative phosphorylation uses a system of oxidoreductase protein complexes (complexes I, II, III, and IV) to transfer electrons during ATP production. Deficiencies in the electron transport chain can result in the leakage of electrons and generate ROS/RNS [40, 41, 106, 107]. Oxidative stress decreases respiratory complex activity, impairs electron transport system, and opens the mitochondrial permeability transition pores leading to cell death [104, 106, 108].

Mitochondria are essentials for the protective actions of melatonin [51, 97, 106, 107, 109–111]. The mechanisms involved include its antioxidant properties and the preservation of complex I and III functions, inhibition of the opening of the permeability transition pores, and the release of cytochrome c. Petrosillo et al. demonstrate that melatonin prevents the opening of the mitochondrial permeability transition pores and its deleterious consequences [51, 110, 112, 113]. We recently reported that melatonin prevents mitochondrial edema, dilation of the ridges, high activity of NADPH oxidase, and apoptosis [97]. Melatonin improves mitofusin-2, which preserves the mitochondrial functional network and prevents apoptosis [114]. The reduction of mitochondrial damage in the heart could be related to the negative regulation of angiotensin II type 1 receptor (AT1) by melatonin [97]. The induction of Hsp70 through melatonin is compatible with an additional mechanism related to Tom 70, a translocase of the outer mitochondrial membrane [97, 115, 116]. The interaction of Hsp70 with Tom 70 initiates mitochondrial import processes [116]. Tom 70 regulates melatonin-induced cardioprotection by preventing mitochondrial deterioration and oxidative stress [97, 115].

Melatonin's cardioprotection associates with an increase in the number of mitochondria and positive regulation of survival genes such as nicotinamide phosphoribosyl transferase and nicotinamide adenine dinucleotide-dependent deacetylases, called sirtuins [117]. Particularly sirtuin-1 and sirtuin-3 are downstream mediators of the cardioprotective actions of melatonin. Sirtuin-1can modulate fatty acid oxidation, apoptosis, oxidative stress, and autophagy through deacetylation of transduction factors like NF-κB, forkhead box class O, p53, peroxisome proliferator-activated receptor alpha, thioredoxin-1, and Bcl-xL [117–121]. Sirtuin-3 is a family member that is primarily located in the mitochondria and protects against inflammation and diseases related to oxidative stress. Melatonin elevates sirtuin-3, stimulates superoxide dismutase activity, and suppresses mitochondrial oxidative stress [31, 117, 122, 123]. Additionally, melatonin protects nuclear and mitochondrial DNA [122, 124, 125]. The multiple actions of melatonin provide potent protection against mitochondrial-mediated lesions.

1.1.4 Melatonin modulates ion channels

Melatonin exerts its electrophysiological effects by multiple mechanisms. One of the ways for melatonin to interact is through the modulation of ion channels. Whether we consider its role as a drug or as a biological molecule, it should be taken into account how melatonin has been considered an electrophysiological modulator for many physiological and clinical conditions such as control of circadian rhythms, regulation of arterial blood pressure and heart rate in mammals, sleep processes, and antiaging, among others. Its role in the modulation of several ion channels is crucial to understand the molecular mechanism underlying the electrophysiological properties as an antiarrhythmic.

Melatonin regulates anionic and cationic selective channels by multiple pathways, at different doses and time-dependent responses. It is important to remember the wide spectrum of action this molecule has. For example, results regarding the pathophysiology of lung fibrosis show that volume-regulated anion

currents do not respond to acute exposure of cells to melatonin in hypotonic solutions [126]. However, when cells are pre-incubated with melatonin concentrations from 1 to 100 μM for 30–60 min, the anionic currents in response to hypotonicity are blunted in a dose-dependent manner. These time- and dose-dependent responses could support the electrophysiological effect during regional ischemia after 20–30 minutes of melatonin exposure in isolated rat hearts, because during ischemia cardiomyocyte swelling activates anionic currents, and melatonin downregulation of these currents is a potential explanation [127, 128]. Additionally, these MT receptor interactions described in fibroblast deserve further evaluation in myocardial tissue.

From the perspective of the interaction between melatonin and its target, it will be crucial to increase the knowledge about the allosteric contact between melatonin and an ion channel. For example, melatonin blocks the potassium channels (Kv1.3) in a reversible manner through the interaction with different binding sites on the human peripheral blood T lymphocytes [129]. However, the inhibitory effects require high extracellular melatonin in the mM range [129]. Cardiomyocytes do not express this specific potassium channel, but a homologous mechanism can exist for other channels waiting to be reported.

Most of the information regarding the role and effect of melatonin in the organisms has been described in the nervous system. One of the most popular is melatonin-related circadian rhythm. In particular, how melatonin influences circadian phase and electrical activity thanks to the interaction with Kir3.x channels presents them as a therapeutic target for diseases related to circadian disruption and melatonin signaling features [130]. In addition, the effects of melatonin in this pacemaker of circadian rhythm could be due also to its modulation of inwardly rectifying potassium channels (Kir3.1/Kir3.2) via MT1 receptors [131]. Moreover, melatonin is also necessary for circadian regulation of sleep. This effect was described to be driven by the suppression of GABAergic neurons by melatonin in the lateral hypothalamus (crucial function for wakefulness), via interaction with MT1 receptor in order to inactivate hyperpolarization-activated cyclic nucleotide-gated channels [132].

Melatonin is a potential neuroprotective molecule thanks to its interaction in a mitochondrial pathway involving the closing of permeability transition pore and opening of ATP sensitive potassium channels (KATP) [133]. The opening of KATP contributes to melatonin antiseizure effect [134]. The preventive actions on the permeability transition pore have been reported in myocardial tissue as well [51, 112, 113]. However, opening of KATP channels with high concentrations of melatonin could be proarrhythmic [135, 136].

Melatonin modulates most of the voltage-activated calcium channel subtypes (L, P, Q, N, and R) with different effects [137–141]. Melatonin inhibits voltage-dependent calcium entry in cultured rat dorsal root ganglia neurons, regulates calcium entry into pineal cells, and has dose-dependent inhibitory effects on free $[Ca^{2+}]_i$ in mouse brain cells [137]. Melatonin has no effect on voltage-activated calcium channels in cultured human aortic smooth muscle cells [141]. Melatonin accutelly increase L type calcium currents in chick cardiac membranes [140, 141]. An early study shows that melatonin downregulates voltage-sensitive calcium channels in the heart [142]. These results indicate that melatonin may have differnt acute and chronic implications for normal cardiac physiology and for the pharmacological manipulation of the heart [142].

Melatonin mediates vasodilation of cerebral arteries through the activation of large-conductance Ca^{2+}-activated K^+ (BK_{Ca}) channels via both melatonin receptor-dependent and melatonin receptor-independent modes, increasing BK_{Ca} channel current density but not the KV channel current density [143]. Small-conductance

Ca^{2+}-activated K (SK) channels are also modulated by the action of melatonin [144]. Upregulation of SK channels plays a role in memory loss and indicates that melatonin reverses memory deficits in rats by downregulation of SK1, SK2, and SK3 channels in their hippocampi [144].

Additional information was brought about KCNQ from the aorta and related with vascular tone, and KCNH2 in the left ventricle was associated with QT duration in rats where melatonin was able to prevent the increase in blood pressure and change KCNQ and KCNH2 gene expression profiles [145].

Melatonin effects on connexin proteins will be extensively analyzed in the second and third sections of the chapters for its proven relationship with both acute and chronic antiarrhythmic effects of melatonin.

1.2 Electrophysiology and arrhythmias

The heart pumps blood under a synchronized electrical control. Arrhythmias are the electrical problems in the rhythm of the heart. The heartbeats may be faster in the case of tachyarrhythmia and slower in bradyarrhythmia.

Fatal arrhythmic events follow a circadian pattern [2]. Arrhythmogenesis decreases during nighttime when the melatonin levels increase 30 to 70 folds. Life-threatening cardiac arrhythmias (ventricular tachycardia, ventricular fibrillation, and sudden cardiac death) are more likely to occur in the morning after waking. Arrhythmias also increase with age and heart diseases [146–148].

Disturbances in membrane excitability or conduction cause arrhythmias. Excitability manifests as action potentials and involves coordinated ion movements across the cell membrane through ion channels, exchangers, and ATPases [149]. Conduction is the propagation of bioelectrical signal throughout the heart. Action potentials automatically originate at the sinoatrial node, spread to the atria, and, after a small delay in the atrioventricular node, rapidly and synchronously activate the ventricles via the His-Purkinje system. Action potentials propagate from cell to cell using low-resistance pathways known as gap junctions. Connexin proteins assemble into intercellular channels at gap junctions. Connexin 43 (Cx43) is the most abundant connexin in the heart [150]. Gap junctions couple the cells and allow the flow of electrical current and small molecules. The largest accumulation of connexins occurs in a specialized structure at the ends of cardiomyocytes called intercalated discs. Cardiac propagation is anisotropic, particularly more rapid in the longitudinal direction of the cell than in the transverse direction. The lateral borders of the myocytes usually show variable amount gap junctions depending on age or disease.

Cardiovascular diseases are the leading cause of death in the world [151]. Most deaths occur suddenly [152]. Catastrophic sudden death events motivate us to search for causes and possible solutions [153]. This is a great scientific and social health challenge. The approaches of recent years have reduced the burden of cardiovascular disease, but there is still much to improve [154]. A case occurs with arrhythmias. The rhythm disorders motivated emergency interventions, especially during the first hour of the manifestation of coronary heart disease. Cardiopulmonary resuscitation, ambulances, and cardiodefibrillation were response strategies to unexpected events. Unfortunately, they are still unexpected due to the limited understanding of the causes at a level that would allow us to predict, avoid, or control the occurrence of an event [155]. In that sense, the strategies that attempt to determine risks grew in order to establish a more efficient direction of interventions [156, 157]. Today they allow us to expect more lethal events in severely ill people. However, risk factors are still far from being effective and much less efficient. The changes that occur in physiology as a result of exposure to different risk factors would be one of the explanations [158].

2. Acute antiarrhythmic mechanisms of melatonin

Melatonin acts at multiple electrophysiological levels due to its receptor-dependent and receptor-independent mechanisms. In 1998, the seminal work of Tan et al. highlighted the antiarrhythmic properties of melatonin [159]. During the past two decades, our understanding of the pleiotropic action of melatonin increased significantly.

The antiarrhythmic effect of melatonin was first attributed to its notable antioxidant properties, mainly because melatonin results were better than those obtained with an ascorbic acid at concentration 10–500 times higher [159]. Numerous studies confirmed antiarrhythmic protection and related it to its remarkable antioxidant properties [160–167].

Our research group corroborated the antiarrhythmic effect of melatonin in isolated hearts of female rats, when administered continuously from the stage prior to the onset of myocardial ischemia [127]. Notably, the antiarrhythmic protection had a dose-dependent response, while the antioxidant capacity was the same for all the doses studied. The preventive effect on the shortening of the action potential that occurs between the 7th and 10th minute of the ischemia was another dose-dependent variable found in our study. This led us to think that the antiarrhythmic mechanism could be due to a lower heterogeneity in the repolarization of myocardial tissue that diminishes the possibility of reentry circuits being formed and maintained. As previously mentioned, the time- and dose-dependent responses could be due to melatonin inhibitory effect against swell-activated anionic currents [126–128].

We recently showed that melatonin reduces arrhythmias when administered during reperfusion, a useful timing for the clinical context of acute coronary syndromes, because most therapies can only start close to the reperfusion period [168]. Melatonin showed protective mechanisms when administered to isolated hearts of rats fed with fructose and spontaneously hypertensive rats. These animals show greater activity of the enzyme NADPH oxidase, which is one of the main systems for generating free radicals, and, therefore, higher levels of oxidative stress. The antiarrhythmic effect was not affected in the models with greater oxidative stress, and in all groups, it was accompanied by a temporary shortening of the duration of the action potential during the first 3–5 minutes of reperfusion. This result was interpreted as a reduction in the ability to generate early and late postdepolarizations. Self-limited arrhythmic events, such as ventricular extrasystoles, salvos, and even non-sustained ventricular tachycardia, occurred in all experimental groups. The main difference was that the hearts treated with melatonin did not show sustained forms of arrhythmias, either sustained ventricular tachycardia or ventricular fibrillation. These results (potential shortening and absence of sustained arrhythmia) are difficult to reconcile with the mechanisms postulated for reentry circuits.

The same year of our publication of the antiarrhythmic protection of melatonin administered in reperfusion, another group published that melatonin protects against arrhythmias, by increasing the threshold to electrically induce sustained ventricular fibrillation, by increasing the myocardial Cx43 by PKC in hypertensive rats [169]. Melatonin prevented myocardial abnormalities of connexin and improved cardiac conduction.

Based in these interesting results, we tested if melatonin could prevent hypokalemia-induced ventricular fibrillation by Cx43 preservation [83]. The acute administration of melatonin during low potassium perfusion reduced the incidence of ventricular fibrillation and improved the recovery of sinus rhythm in those hearts that, despite being treated with melatonin, developed sustained fibrillation. Protection was mediated by the activation of melatonin receptors and by the prevention of dephosphorylation and lateralization of Cx43.

A brief explanation of the electrophysiological changes induced by hypokalemia will help to appreciate the relevance as antiarrhythmic. Severe hypokalemia induces changes in ventricular repolarization, such as lengthening the QT interval, prominent U waves, fusion of T and U waves associated with and increases risk of arrhythmic death [83, 170, 171]. Our experimental model confirmed the lengthening of the QT interval and correlated with an increase in the duration of the action potential [83]. Melatonin did not prevent the prolongation of the action potential induced by hypokalemia when measured at 90% of repolarization but maintained action potential duration at 50% of repolarization and made the membrane potential more stable, showing less after depolarization. Luzindole blunted both effects of melatonin, suggesting the involvement of melatonin receptor activation in the preservation of membrane potential.

Hypokalemia decreases NaK-ATPase activity and causes an intracellular Ca^{2+} overload that facilitates the development of delayed postdepolarizations through the transient inward currents [172–174]. Delayed postdepolarizations are considered triggers of arrhythmias because they can initiate an action potential in isolated cells. However, it is unlikely that an extra action potential can be initiated from a single cell in the tissue due to a mismatch between the current source from the cell and the current sink produced by the surrounding cells [175]. To overcome the source-sink mismatch, there must be a reduced sink through intercellular decoupling or an increase in the source through the synchronization of delayed postdepolarizations between several adjacent cells. Both situations could be assumed based on the results of anisotropic conduction studies and immunofluorescence imaging [83].

In fact, hypokalemia induces conduction abnormalities, increased amplitude and duration of the P wave, a slight prolongation of the PR interval, atrioventricular block, increased QRS duration, and cardiac arrest [173, 176]. We found all these electrocardiographic disorders during our experimental model of hypokalemia [83]. Melatonin prevented the widening of the QRS and delayed activation of the potential for epicardial action. The latter could be considered as a substitute for conduction velocity in complex tissues such as ventricles, assuming unknown routes from endocardial activation points that indicate the onset of QRS to epicardial myocytes recorded with microelectrodes. These improvements in ventricular conduction were related to Cx43 lateralization and dephosphorylation.

The lateralization of connexins has been detected in chronic atrial fibrillation, cardiac hypertrophy, heart failure, and after myocardial infarction [21, 177–179]. An increase in the fraction of lateral connexins that form functional channels improves transverse conduction velocity and contributes to the spread of the arrhythmogenic impulse. High side-by-side lateralization can favor conduction blockage due to mismatches between the source and the sink [175, 180]. A unidirectional block can lead to reentry circles that result in tachycardia or ventricular fibrillation [181]. Therefore, the acute lateralization induced by hypokalemia is an important arrhythmogenic factor [83]. It is noteworthy that melatonin prevented acute lateralization of Cx43.

Connexin 43 phosphorylation could lead to better coupling or uncoupling depending on the target amino acid, but dephosphorylation is clearly associated with uncoupling [21, 177, 182]. It is not yet known whether the dephosphorylation of Cx43 during low potassium is the result of increased phosphatase activity and/or an increase in phosphokinase or what are the intracellular mechanisms that prevented dephosphorylation when treated with melatonin. Dramatic reductions in intercellular communication due to the loss of phosphorylated Cx43 and the accumulation of non-phosphorylated Cx43 were previously reported in other experimental models [177].

Our results could be relevant mainly in those situations in which acute hypokalemia can be anticipated as in dialysis [183, 184]. Both QT interval and the QT dispersion increase after dialysis. We propose that melatonin could make the heart

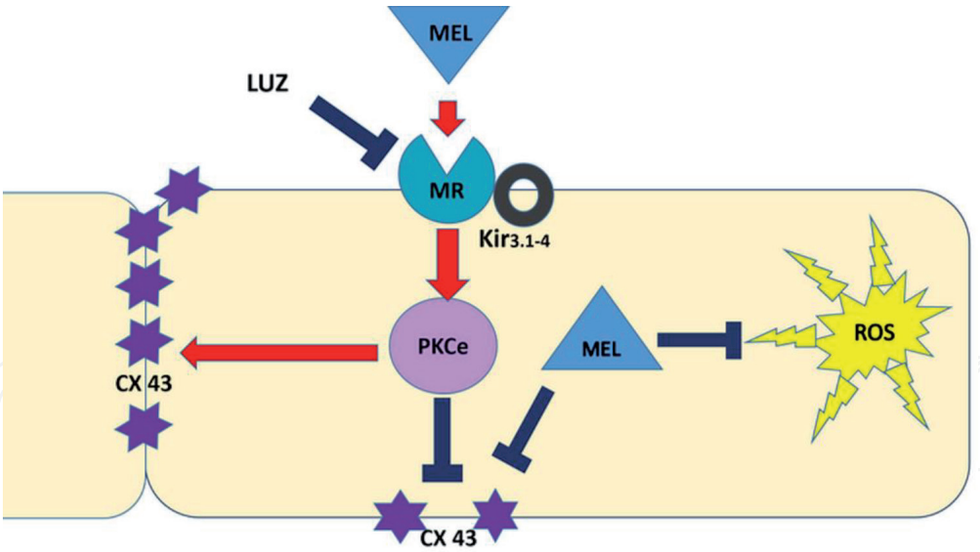

Figure 1.
Acute antiarrhythmic mechanisms of melatonin. The red arrows indicate stimulation, and the interrupted blue lines indicate blockage.

more resistant to arrhythmic events triggered by rapid changes in plasma electrolyte concentrations, regardless of a lack of effects on the ECG. In addition, those dialysis patients also suffer from disorders in the circadian rhythms and low levels of melatonin [185]. However, clinical translations of our results should be done with caution, mainly because we use a high dose of melatonin administered directly to the heart. Based on melatonin's pharmacokinetics in humans, to achieve a similar concentration in plasma to the one tested *ex vivo*, a dose 10 times higher the highest intravenous dose tested until now should be administered [186, 187].

Melatonin has a remarkable antiarrhythmic activity that is carried out based on actions dependent on and independent of receptor activation. To summarize we propose that the antiarrhythmic effect of melatonin is mediated by receptor activation beyond its outstanding antioxidant actions (**Figure 1**). The shortening of the action potential could be associated with the activation of MT1 melatonin receptors, since they can regulate specific ion channels such as Kir3.1 channel. MT1 and MT2 receptors could indirectly modulate other electrophysiological effects through intracellular signaling such as decreased cyclic adenosine monophosphate, increased phospholipase C, and PKC activation.

3. Chronic antiarrhythmic mechanisms of melatonin

Endogenous melatonin would be an intrinsically protective factor with therapeutic potential [188, 189]. Melatonin is a promising treatment for cardiovascular diseases such as myocardial ischemia/reperfusion injury, hypertension, and heart failure. It has been shown that melatonin levels were reduced in patients with acute myocardial infarction and in patients undergoing primary coronary angioplasty [190]. These findings suggest that melatonin could play an important role in preventing ischemia/reperfusion heart injury. Indeed, reperfusion arrhythmias increase in pinealectomized animals, suggesting a protective role of endogenous physiological melatonin levels [163, 189].

Chronic melatonin supplementation, either in physiological or pharmacological ranges, protects against arrhythmias [8, 21, 97, 163, 169, 189, 191, 192]. Beyond the reported antioxidant properties of melatonin, it reduces severe ventricular

arrhythmias by antifibrotic mechanisms, electrical remodeling, direct mitochondrial protection, myocardial Cx43 preservation via PKC signaling, and vitamin D-HSP70/AT1 counterbalance (**Figure 2**). Its cardioprotective properties persist in relevant cardiovascular risk factor models like hypertensive, obese, and nephropathic rats. The latter is interesting because most of the therapeutic interventions postulated so far fail to be reproduced under risk factor conditions.

A preventive approach would be of great value in the face of unpredictable acute arrhythmic events, especially if the intervention manages to avoid the most severe and potentially lethal arrhythmias such as ventricular tachycardia and fibrillation. Numerous efforts have been made in that direction. In the last quarter of the twentieth century, several antiarrhythmic drugs were tried, but most of them showed a proarrhythmogenic profile or failed to reduce mortality [193–196]. A time of great progress was appreciated with the introduction of implantable cardiodefibrillators. However, surgical intervention and high cost limit its population efficiency. A strategy to improve the availability of preventive interventions is to select potential beneficiaries based on their risk of serious events. This would compensate for potential side effects and optimize the investment of resources. Other strategies, such as vaccines, are based on achieving the greatest possible scope with the least number of interventions that attenuate the severity of diseases. In the case of arrhythmias, we still have no clear "antiarrhythmic vaccine." Therefore, risk-oriented strategies would be an acceptable approach.

From a preventive point of view, the pleiotropic protection mechanisms of melatonin could effectively limit the arrhythmic complications associated with hypertension [21, 169]. Arterial hypertension causes vascular deterioration, overloads the heart, and predisposes to a greater number of arrhythmic events. More than five decades ago, it was reported that surgical removal of the pineal gland, a procedure that essentially eliminates circulating levels of melatonin, was followed by a slow but persistent increase in blood pressure in rats [197]. This finding has been confirmed in several subsequent studies [11]. In addition, daily treatment of pinealectomized rats with melatonin attenuated the elevation in blood pressure

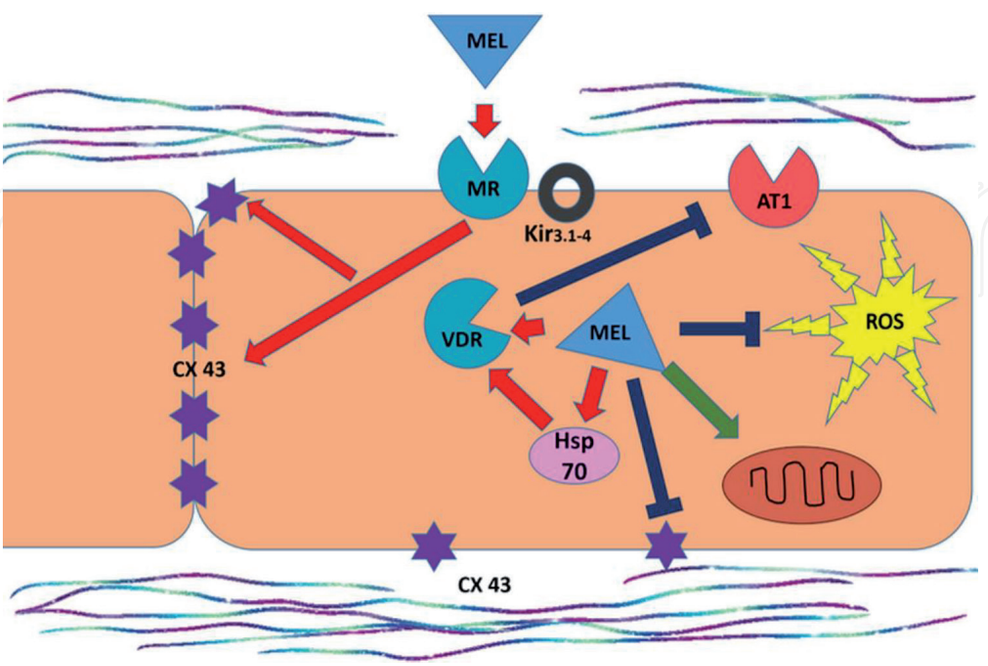

Figure 2.
Antiarrhythmic mechanisms of chronic melatonin administration. Extracellular lines represent reduced fibrosis after melatonin treatment. The red arrows indicate stimulation and blue ones show blockage. The green arrow marks direct mitochondrial protection.

that accompanies pinealectomy [198, 199]. Potentially related to these experimental findings are those observational studies in humans that document an age-related gradual increase in blood pressure [7]. Of special interest is that the ability of the pineal gland to produce melatonin is compromised during aging so that the levels of melatonin in the blood at night gradually decrease [28, 30, 110]. An implication of these findings is that the loss of melatonin during aging can contribute to gradual hypertension and arrhythmias.

The structural remodeling of the myocardium that follows hypertension (mainly cardiomyocyte hypertrophy and fibrosis) is accompanied by changes in the expression, distribution and function of the ionic channels of the cell membrane and the intercellular channels constituted by Cx43 [21, 191, 200]. Remodeling predisposes to life-threatening ventricular tachycardia and ventricular fibrillation by early or late postdepolarization and reentry. Melatonin prevents changes in ventricular redistribution of Cx43 and reduces arrhythmia inducibility [8, 21, 147, 191].

Another chronodisruptor that increases arrhythmic risk are kidney diseases. Chronic kidney diseases (CKD) alter the nocturnal secretion of melatonin [185, 201]. Melatonin levels correlate negatively with the intrarenal activity of renin-angiotensin II-aldosterone system (RAAS) [202]. Melatonin improves intrarenal RAAS in the 5/6 nephrectomy rat model and reduces blood pressure, oxidative stress, and interstitial fibrosis in the remaining kidneys [203].

Renal diseases cause cardiovascular and electrolytic remodeling that increases the risk of arrhythmias [204–206]. Cardiovascular events occur more frequently in patients with chronic kidney disease. Ventricular arrhythmias are particularly prevalent among patients with CKD, even when those patients do not suffer from any electrolyte imbalance [207]. The risk of mortality also increases in patients with CKD who suffer from an acute coronary syndrome [208]. We demonstrated that unilateral ureteral obstruction caused a cardiac remodeling that was accompanied by an increase in reperfusion arrhythmias [209].

The electrophysiological properties of chronic melatonin deserve attention, due to their relevance for cardiorenal situations with high arrhythmic risk and lack of treatments. We recently confirmed the antifibrotic, antiapoptotic, and antioxidant effects of melatonin and linked them to an HSP 70-VDR/AT1 counterbalance which prevents kidney damage and arrhythmogenic remodeling of the heart [97].

In renal and myocardial tissue, melatonin increased HSP 70 and VDR and decreased AT1 and fibrosis. Melatonin increases HSP 70 and protects the liver of rats exposed to toluene from cytotoxicity induced by oxidative stress [100]. HSP 70 regulates antioxidant responses to cellular oxidative stress and reduces NADPH oxidase activity and expression [210]. We demonstrated a myocardial increase in HSP 70 in rats treated with melatonin. HSP 70 induces VDR and facilitates intracellular localization of active vitamin D metabolites and transactive VDRs [209, 211, 212]. Nuclear melatonin receptors, as members of retinoid-related orphan receptors, may interact and prevent degradation of VDR [97, 103]. Expression of myocardial VDR links chronic kidney disease with cardiovascular disease due to the reduction in VDR that amplifies the effects of angiotensin [212]. Melatonin decreases renal and myocardial overexpression of AT1 [97]. It is well documented that the AT1 pathway leads to myocardial fibrosis during CKD [97]. As previously suggested, the low expression of AT1 through VDR induction could be a consequence of HSP 70-mediated cellular protection [213]. Angiotensin II exerts a tonic modulation of melatonin synthesis by influencing the activity of tryptophan hydroxylase through AT1 supporting the postulated feedback (or reciprocal regulation) between AT1 and melatonin [97, 202].

Additionally, the mitochondrial dynamics relates to the RAAS. We show that melatonin prevents mitochondrial edema, high activity of NADPH oxidase, and

apoptosis. In this sense, the reduction of mitochondrial damage melatonin could be related to the negative regulation of AT1. The induction of HSP 70 through melatonin is compatible with an additional mechanism related to Tom 70. Furthermore, Tom 70 regulates melatonin-induced protection against myocardial infarction [115, 116]. All these data allow us to assume that the induction of HSP 70 by melatonin and the reduction of AT1 are critical components of the cellular stress response.

We attribute the higher vulnerability to ventricular fibrillation during reperfusion in the kidney disease rat model to the prooxidative and profibrotic changes that accompanied the increase in AT1 and the decrease in HSP 70 [97, 209]. Myocardial oxidative stress—particularly in the mitochondria—and fibrosis are well-known proarrhythmic substrates [55, 71]. Free radicals act as triggers for the beginning of arrhythmic events. The persistence of high-frequency rhythms requires reentry circuits [214]. Altered conduction and shortening of the action potential contribute to the complex reentry mechanisms involved in ventricular fibrillation.

Melatonin protection against myocardial remodeling induced by kidney disease is one of the factors that protect against ventricular fibrillation. Chronic melatonin prolongs the action potential duration and hyperpolarizes the cardiomyocytes. These changes are the first report of myocardial action potential modifications by chronic administration of melatonin. Opening of Kir3.x channels by melatonin receptor activation could explain hyperpolarization [131]. The action potential lengthening is harder to explain because melatonin activates currents involved in the action potential repolarization and the only inhibitory effect of melatonin against outward potassium currents was described in neurons [90, 129, 130, 215–217]. As previously mentioned, the downregulation of volume-activated anionic currents can explain attenuated response to action potential shortening induced by ischemia [126].

A synthesis of the mechanisms of protection of chronic treatment of melatonin cardiovascular complications is outlined in **Figure 2**. We focus our attention on the preventive effects of melatonin against the alteration of Cx43, mitochondrial oxidant capacity, and membrane potentials. In addition, modulation of the AT1 and VDR receptors related to the increase of HSP 70 contributes to the cardioprotective effects of melatonin.

4. Conclusions

Melatonin is the rhythmic protector of healthy heart rhythm and a promising preventive agent against ventricular fibrillation, the most lethal and disorganized heart rhythm. Pleotropic effects of melatonin make it an exceptional acute and chronic antiarrhythmic.

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Conflict of interest

The authors declare no conflict of interest.

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