Multiple Functions of Melatonin in the Military Setting

Subjects: Pharmacology & Pharmacy

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Melatonin is a technique that is being increasingly employed to manage growing psycho-physical loads. In this context, melatonin, a pleotropic and regulatory molecule, has a potential preventive and therapeutic role in maintaining the operational efficiency of military personnel. In battlefield conditions in particular, the time to treatment after an injury is often a major issue since the injured may not have immediate access to medical care. Any drug that would help to stabilize a wounded individual, especially if it can be immediately administered (e.g., per os) and has a very high safety profile over a large range of doses (as melatonin does) would be an important asset to reduce morbidity and mortality.

Keywords: melatonin ; military combat personnel ; heart rate variability

1. Introduction

Melatonin is an antioxidant/anti-inflammatory agent estimated to be 3 billion years old, and it probably evolved in bacteria. The blood levels of melatonin, which exhibit a circadian rhythm, are derived from the pineal gland. These levels are defined as central endogenous melatonin. One of the major actions of this kind of melatonin is influencing 24-h variations in organismal physiology. Additionally, however, there is also peripheral endogenous melatonin, which is produced in the mitochondria of many—perhaps all—cells. The main action of peripheral melatonin is likely to protect the mitochondria from damage due to locally generated oxygen and nitrogen-free radicals. Melatonin, together with its metabolites, which are also radical scavengers, is a powerful antioxidant present in all living organisms, including animals and plants.

2. Metal-Chelating Activity of Melatonin as Protection from Chemical and Radioactive Weapons

2.1. Chelating Activity of Melatonin: An Overview

Environmental pollution is considered a significant threat to human health due to the toxic effects of a variety of organic and inorganic pollutants [1]. Heavy metals comprise a major category of toxic environmental pollutants. An increasing body of data demonstrates that armed conflicts and military activity contribute significantly to environmental pollution [2]. A significant accumulation of metals has been observed in battlefields areas, small-arm shooting ranges, artilleries, mortar and rocket ranges, and grenade courts [3]. Military-related metal emissions therefore pose significant health hazards to military personnel, with the potential for overexposure. Occupational exposure to heavy metals can lead to the onset of various diseases, such as cardiovascular problems, neuronal damage, kidney damage, and an increased risk of cancer and diabetes.

2.2. Melatonin to Counteract Cellular Toxicity Induced by Heavy Metals

There are several mechanisms by which heavy metals induce cellular toxicity, but the main mechanism is the production of reactive oxygen species (ROS) that cause cellular oxidative damage [4]. Melatonin is highly effective in reducing such oxidative stress, as proven in a large number of reports. Its protective actions are the result of several means: the direct detoxification of ROS and reactive nitrogen species (RNS), the stimulation of antioxidant enzymes, and the suppression of other free-radical-generating enzymes. Additionally, melatonin also chelates transition metals, which are involved in the Fenton/Haber–Weiss reactions; due to its metal-chelating ability, melatonin reduces the formation of the highly reactive hydroxyl radical (•OH), which probably accounts for more than 50% of the oxidative stress that cells sustain [5]. Evidence shows that melatonin reacts with a number of metal ions, resulting in the formation of stable metal complexes. For example, using absorption voltammetry as a means of evaluation, it has been shown that melatonin, in proportion to its concentration, binds several heavy metals, including aluminum, cadmium, copper, iron, lead, and zinc, similar to metallothionein [6]. Melatonin chelates both iron (III) and iron (II), participating in the Fenton reaction to generate •OH. Melatonin is able to restore the biological activity of hemoglobin by acting on highly covalent iron and transforming it into iron (III), and it also reduces •OH, which is highly toxic.

2.3. Melatonin in Cerebrospinal Liquid (CSF): A Very Powerful Antioxidant

The important biochemical actions of melatonin are more effective than those carried out by metallothioneins, as the latter, being proteins, could be damaged by free radicals when they bind to transition metals. In comparison, melatonin neutralizes the generated free radicals, and thereby limits molecular and cellular damage. This is especially important in the brain, where metallothionein functions as a reducing agent when it binds metals. High levels of melatonin in the cerebrospinal fluid (CSF), and, consequently, in the brain, are important to ensure adequate protection against regional oxidative stress. In the brain, melatonin, via its direct scavenging activity and indirect antioxidant actions, significantly reduces the neural accumulation of oxidatively damaged molecules and seemingly compliments or replaces metallothionein as the major binder of transition metals.

2.4. The Journey of Melatonin in the Human Brain

Historically, the direct release of pineal melatonin into the rich pineal capillary bed has been accepted as the primary route of secretion. In reference to the central nervous system, however, the most important route of melatonin delivery may be its release via the pineal recess directly into the CSF of the third ventricle (3V). From the 3V, melatonin eventually moves with the CSF into the subarachnoid space that surrounds both the brain and spinal cord from where it has ready access to the neural parenchyma. Concentrations of melatonin in CSF increase rapidly at the onset of darkness and drop dramatically in the presence of light. Significant quantities of free radicals are produced in the brain due to the high metabolic demands of this organ, and in particular due to the high demand for oxygen, the parent molecule that produces numerous free radicals from its metabolism. The elevated levels of melatonin in the CSF, and therefore in the CNS, ensure shielding it from oxidative stress [7][8][9].

2.5. Melatonin as Copper's Direct Chelator

The activity of melatonin and its metabolites cyclic 3-hydroxymelatonin (c3OHM), N1-acetyl-N2-formyl-5-methoxykinuramine (AFMK), and N1-acetyl-5-methoxykinuramine (AMK) in chelating metals has recently been analyzed [10]. When present in high intracellular concentrations, copper generates the •OH previously mentioned. Melatonin and its three metabolites produce stable complexes with copper ions. The direct chelation mechanism (DCM), compared with that of deprotonation–chelation, has been found to be a highly efficient chelation pathway of Cu (II) for melatonin and each of its metabolites. Furthermore, the melatonin/metabolite complex adequately interferes with the initial phases of the Haber–Weiss reaction, thus reducing the generation of highly oxidizing •OH. In consideration of these findings, Galano et al. [10] realized that melatonin, in addition to being the parent molecule in the free-radical-scavenging cascade [11], plays an essential role in metal chelation.

2.6. Principal Mechanism of Metal Toxicity

A review was recently published describing the molecular damage to organisms caused by metals and the ability of melatonin to chelate these harmful substances [12]. This entry summarized, in detail, the toxicity mechanisms of a number of heavy metals. The authors remind the reader that some metals are crucial to a wide variety of biological processes. In comparison, some xenobiotic metals, which lack physiological functions, interact with biological macromolecules and cause oxidative damage. These damaging agents include aluminum, cadmium, lead, mercury, and the metalloid arsenic. Although the molecular mechanisms are not fully understood, the main biochemical mechanisms by which heavy metals disrupt cellular homeostasis are described in significant detail [13].

2.6.1. Cadmium and Melatonin

Cadmium (Cd^{2+}) is a ubiquitous environmental contaminant that is ingested in drinking water and food and inhaled during breathing. High concentrations of cadmium are found in cigarettes, and Cd^{2+} is classified as a Class 1 human carcinogen [14].

In addition to direct scavenging and the indirect augmentation of the activities of antioxidative enzymes, in an in vivo study, melatonin was found to lower kidney Cd^{2+} accumulation [15]. This reduction in intracellular Cd^{2+} levels requires melatonin (i) to cross renal cell membranes [16], which it does due to its lipophilic character, permitting the removal of Cd^{2+} (ii) to establish stable complexes with Cd^{2+} or (iii) to the inhibit intestinal absorption of Cd^{2+}, which would reduce the total body load of this damaging metal.

2.6.2. Mercury and Melatonin

Mercury is a ubiquitous contaminant in the environment, making it very difficult for humans to avoid. It is considered a highly dangerous environmental pollutant. Humans and animals can come into contact with various forms of mercury,

including elemental mercury (Hg) vapors, inorganic mercury [Hg (I)], mercury [Hg (II)], and organic mercury compounds [17]. There are several mechanisms by which these compounds alter the functioning of cells. Mercuric ions are able to bind to all molecules containing a thiol, such as glutathione (GSH), cysteine, metallothioneins (MTs), homocysteine, N-acetylcysteine (NAC), and albumin [18][19]. Consequently, the antioxidant cellular mechanisms resulting from exposure to this pollutant are altered [20].

2.6.3. Melatonin against Mercury's Neurotoxicity

Melatonin detoxifies numerous ROS including hydrogen peroxide (H_2O_2), hydroxyl radical (•OH), peroxyl radicals (ROO•), and singlet oxygen ($^1O_2$), in addition to RNS, including nitric oxide radicals (NO•) and peroxynitrite ($ONOO^-$) [21]. Some or all of these are involved in the toxicity of mercury. The ability of melatonin to lower the neurotoxicity of mercuric chloride in animal studies has been shown. Similarly, since mercury poisoning is a proposed cause of Alzheimer's disease [22], further documentation of the efficacy of melatonin in reducing mercury-induced neural damage has long-range implications for military personnel.

2.6.4. Arsenic and Melatonin

The metalloid arsenic (As), which exists mainly in two biological oxidation states, arsenite [As (III)] and arsenate [As (V)], is a natural environmental contaminant with well-documented carcinogenic activity [23]; the trivalent forms of arsenic are considered the most dangerous [24]. They interact with sulfhydryl groups of proteins and inhibit many cellular biochemical reactions. The pentavalent forms are less toxic and act at the level of oxidative phosphorylation. Human beings can come into contact with both trivalent and pentavalent forms. The formation of numerous ROS/RNS in the metabolism of arsenic has been documented [25]. Consequently, the depletion of GSH due to consumption induced by the metabolism of As determines the establishment of an oxidizing intracellular environment, which is the basis for the process of carcinogenesis. Furthermore, reductions in antioxidant enzymes, including superoxide dismutase (SOD) and catalase (CAT), have been observed in vitro after exposure to As [26].

2.6.5. Lead and Melatonin

Lead is known to damage vital organs and suppress cellular processes. The major target organ of this heavy metal, in terms of toxicity, is the brain. The neurotoxicity of lead is expressed by altering the blood–brain barrier, astrocytes, and endothelia of the cerebral microcirculation [27]. Its accumulation occurs mainly at the hippocampal level, although all brain regions can be affected. Similarly to other heavy metals, pathogenetic actions are also multifactorial for lead, increasing the level of oxidative stress, altering the functioning of numerous enzymes, and inhibiting the absorption of trace elements, such as calcium and zinc [28].

2.6.6. Melatonin and Lead-Induced Neurological Damage

Melatonin has been used in several situations to overcome lead toxicity. In rats, melatonin almost completely reduced the neurological damage caused by lead, thus exerting an important neuroprotective action by restoring the endogenous levels of GSH and SOD throughout the brain [29]. Furthermore, melatonin exerted a neuroprotective action, also acting positively on structural damage and on the reduction in neuronal density caused by lead. In addition to its important antioxidant action, further mechanisms involved in neuroprotection have been described, such as interaction with calmodulin, blocking increases in intracellular Ca^{2+}, changes in gene expression, and the improved efficiency of mitochondrial oxidative phosphorylation. In cultured human neuroblastoma cell line SH-SY5Y, melatonin also restored lead-reduced GSH levels and protected against apoptosis by inhibiting caspase-3 activation [30].

2.7. Metal-Chelating Activity of Melatonin: Concluding Remarks

The military, due to their peculiar work activity, can be exposed to heavy metals. For this reason, logistical strategies should be implemented to reduce or eliminate possible sources of occupational exposure to heavy metals. However, especially in military operations abroad, this is not always controllable. In this context, the administration of melatonin can represent a very interesting primary prevention strategy against professional exposure to heavy metals, both for its beneficial biochemical actions, and also due to its very high pharmacological safety profile. Melatonin is a non-enzymatic antioxidant (i.e., the antioxidant H) able to deactivate the ability of heavy metals that trigger oxidative processes [31]. The melatonin/metal complex follows the organometallic rules for ligand–metal coordination, that is, the rule of the 18 electrons (16 electrons for 'platinum metals', such as Ni^{2+} complexes) and the generation of tetrahedral, octahedral, or square planar structures.

2.8. Melatonin for Protection from Chemical Weapons

Chemical warfare agents (CWAs) are substances that incapacitate a person and can kill them, mainly causing neurological damage, but also to the destruction of other organs. Currently available decontamination methods make it essentially impossible to quickly decontaminate a site after CWA exposure. Additionally, there are no completely effective antidotes or treatments against these agents after individuals are exposed to CWAs. Considering the complexity of the physiological processes that occur after exposure to CWAs, melatonin may be a useful antidote and may provide a reasonable strategy to counteract CWA-induced injuries [32].

2.9. Melatonin against Mustard Gas Toxicity

Oxidative stress and intracellular molecular damage are the main pathogenetic mechanisms behind the toxicity of blister agents such as mustard gas, chlorine, and phosgene. An interesting in vivo study evaluated the role of melatonin as an antidote in acute mustard gas intoxication. The most reliable parameter to test the serious nature of the exposure was the level of total plasma protein carbonyls. The carbonyl levels were significantly increased due to mustard gas contamination, and carbonylation was slowed due to melatonin intake. Carbonyl groups are a generic oxide production of biomolecules, and their formation on proteins is considered a severe, oxidative, and generalized stress marker. Melatonin has proven to be a prospective compound for reducing mustard gas toxicity damage in rats [33].

2.9.1. Mustard Gas as an Invalidating Agent: The Role of Melatonin in Acute Toxicity

Sulfur mustard (SM), also known as mustard gas, is a widely used chemical agent. SM is used as a disabling and incapacitating agent rather than to cause death. Melatonin has been shown to be useful in acute MS toxicity through various mechanisms of action, including the ability to repair DNA damage and restoring the correct production of cellular energy at the mitochondrial level.

2.9.2. Mustard Gas as an Invalidating Agent: The Role of Melatonin in Chronic Toxicity

The pathogenetic mechanisms behind the delayed toxicity of mustard gas (i.e., the harmful effects that occur over time after acute exposure) are not particularly clear. However, the epigenetic perturbations caused by MS appear plausible [34]. The term epigenetic describes the possibility of changes in gene expression caused by environmental factors in the absence of changes in the genome sequence. Consequently, the biochemical–molecular mechanisms that encode information beyond the basic DNA sequence and that can be transmitted through mitosis and meiosis form the basis for epigenetic gene regulation. Consequently, the biochemical–molecular mechanisms that encode information beyond the basic DNA sequence and that can be transmitted through mitosis and meiosis form the basis for epigenetic gene regulation.

2.10. Melatonin for Protection from Chemical Weapons: Concluding Remarks

Current knowledge on epigenetic regulation mainly focuses on two molecular mechanisms: histone modification and DNA methylation. It should be remembered that the beneficial action of melatonin in patients with advanced cancer also seems to derive from the combined effects of these two epigenetic mechanisms. In an in vitro study, the data showed that, in high concentrations, melatonin modulates P53 and Bax/Bcl-2 expression [35]. In addition, it is presumed that melatonin inhibits DNA methyltransferases (DNMTs); this is a family of enzymes that methylate DNA at the carbon-5 position of a cytosine residue [36]. There is evidence of the direct epigenetic actions of melatonin on various cellular targets, including histone acetylation enzymes [37]. Melatonin significantly increased mRNA expression for various HDAC isoforms and histone H3 acetylation in neural stem cell lines. Melatonin, as a whole, has non-genomic, genomic, and epigenetic actions. These important biochemical actions of melatonin can be very useful for both acute and delayed mustard toxicity. Romero et al. [38] summarized the cellular and molecular mechanisms displayed by melatonin against CWAs.

2.11. Melatonin as a Radioprotective Agent

Ionizing radiation causes harmful effects to cells through both direct and indirect mechanisms. The cellular molecules sensitive to this form of radiation are damaged by direct action. The indirect effects—which represent about 70% of the overall damage—consist of a pathological interaction with the water molecules that determine the formation of important quantities of free radicals, such as •OH, •H, and eaq−. This, in turn, causes alterations in the subcellular structure. Due to its remarkable antioxidant capacity, melatonin represents an important molecule with radioprotective function. Many studies, both in vitro and in vivo, have confirmed that melatonin protects mammalian cells from the toxic effects of ionizing radiation. Furthermore, numerous clinical studies in the oncology field have documented that the administration of melatonin, also in combination with radiotherapeutic agents, determines a favorable efficacy/toxicity ratio in the treatment

of human cancers [39]. It is believed that most of the tissue damage caused by ionizing radiation (about 60–70%) is attributable to •OH, which melatonin quickly neutralizes [40].

2.12. Melatonin Reduces Genetic Damage from Exposure to Ionizing Radiation

Among the DNA bases, guanine is the most susceptible target to oxidative damage mediated by free radicals, including •OH. In addition to DNA, free radicals also interact with lipids, causing the formation of hydroperoxides [41]. In recent years, the •OH-scavenging ability of melatonin has been tested to evaluate the radioprotective capacity of this molecule. In vivo studies have demonstrated the efficacy of melatonin as a radioactive protector in a dose-dependent manner. For example, Vijayalaxmi et al. observed that the exposure of CD2-F1 mice to 815 cGy of ionizing radiation (LD50/30 dose that kills 50% of mice in 30 days) resulted in a survival rate of 45–50% after 30 days; pretreatment with melatonin at a dose of 125 mg/kg bodyweight increased survival to 60%, while melatonin at a dose of 250 mg/kg bodyweight further increased survival to 85% [42].

2.13. The Role of Melatonin before Exposure to Radiation

This group also found that mice pretreated with 5 or 10 mg/kg of melatonin 1 h prior to radiation exposure showed significantly reduced genetic damage in bone marrow cells, with the 10 mg dose being more effective than the 5 mg dose [43]. The scavenging efficiency of melatonin, together with its indirect antioxidant properties, is documented in numerous independent research articles (over 900 publications in the literature).

2.14. Melatonin as a Radioprotective Agent: Concluding Remarks

As soon as exposure occurs, people—even if they live far from the primary event—could protect themselves through the oral administration of melatonin. This can be repeated several times depending on the specific case and under medical indication. Finally, the toxic side effects of melatonin are none or minimal at most. It is important to evaluate the full potential of melatonin as a radioprotective agent in day-to-day life, as well as in extraordinary conditions, including military settings in the event nuclear weapon use.

3. Melatonin for Psycho-Physical Performance of Flight Force

3.1. Melatonin and Cardiovascular Oscillations

Maintaining physiological cardiovascular oscillations is of great importance for maintaining optimal health. Simultaneous recordings of arterial pressure (AP) and sympathetic nervous system (SNA) activity in both animals and humans through spectral techniques revealed the presence of spontaneous oscillations of the aforementioned signals at slower frequencies than respiratory movements. Of particular interest are the so-called Mayer waves (corresponding to the “10-s rhythm” or 0.1 Hz in humans). The Mayer wave can be defined as the physiological oscillation of arterial pressure (AP) in synchrony with the sympathetic nervous system (SNA) [44]. AP oscillations that satisfy this requirement have a characteristic frequency of ~0.1 Hz in humans [45]. A common feature of Mayer waves is that their frequency is fairly stable within a given species. In particular, it has been shown in humans that this frequency does not depend on sex, age, or posture [46]. These oscillations in the 0.1 Hz frequency range are mainly determined by the baroreceptor and chemoreceptor reflex control system [47]. A method for opening the baroreflex loop is to interrupt the sympathetic transmission at the vascular neuroeffector junction. The reflected origin of these waves has been demonstrated through the use of phentolamine as an antagonist of alpha-adrenergic receptors, which strongly depressed both the Mayer wave and the oscillations of the autonomic nervous system [48].

3.2. Melatonin’s Epigenetic Actions

Hemodynamic oscillations related to Mayer waves have been demonstrated in human cerebral circulation [49]. The pineal gland, by means of its secretory product melatonin, has been implicated in the modulation of the cardiovascular system. Melatonin improves the baroreflex response in correlation to its antioxidant effects [50]. Melatonin influences vascular reactivity [51]. MT1 receptor activation causes vasoconstriction; in contrast, MT2 receptor activation causes vasodilation [52]. The most interesting mechanism by which melatonin can improve physiological cardiovascular oscillations is probably its epigenetic action on the adrenal glands and the heart. Melatonin modifies the genetic expression of NR3C1, the glucocorticoid receptor, in the adrenal gland and the heart [53]. In particular, melatonin reduces the NR3C1 gene in the heart and increases it in the kidneys and lungs. This has several clinical implications, such as increased resistance to hypoxia and improved neuro–cardio–respiratory resonance.

3.3. NR3C1 Gene and Stress Management

In mice, blocking the glucocorticoid receptor in cardiomyocytes and vascular smooth muscle cells resulted in major changes in the structural, functional and biochemical maturation of the fetal heart, thus indicating that the glucocorticoid signaling pathways activated by this receptor are vital for the normal structural and functional development of the heart [54]. In a noteworthy in vivo study on full-term infants, the methylation of the NR3C1 gene was found to be associated with an increase in cardiac variability expressed as RSA (respiratory sinus arrhythmia), and therefore, they had a greater ability to manage stressful events [55].

3.4. The Heart as a Door to Evaluate the Autonomic Nervous System

Heart rate variability (HRV) is a widely used parameter to assess autonomic nervous system (ANS) activity and balance between the sympathetic and parasympathetic branches. One measure of HRV is respiratory sinus arrhythmia (RSA), which identifies heart rate variability that coincides with breathing and reflects parasympathetic control [56]. Prolonged exposure to stress is associated with an autonomic imbalance, that is, a hyperactive sympathetic system and a hypoactive parasympathetic system [57]. NR3C1 is probably the most studied gene in human behavioral epigenetic research. There are a number of reports describing the differences in DNA methylation of the NR3C1 gene to cortisol reactivity and the hypothalamic–pituitary–adrenal (HPA) axis response [58]. Epigenetic modifications of NR3C1 can affect the autonomic nervous system; particularly, an increased methylation of the NR3C1 exon 1F at CpG sites 12 and 13 may be associated with an activation of the parasympathetic pathways with a consequent increase in RSA. It would be interesting to evaluate the possible effects of the exogenous administration of melatonin on cardiac variability expressed as RSA. Historically, melatonin has been repeatedly shown to impact heart and cardiovascular function. A more efficient autonomic modulation may have a positive impact on the psycho-physical performance of military personnel in terms of the prevention of chronic degenerative pathologies and also in terms of a better response to complex stimuli.

3.5. Melatonin and Heart Rate Varibility—HRV

Heart rate variability (HRV) can be defined as the physiological variation in the time interval between heartbeats. Both heart rate and cardiac output are influenced by the efferent vagus nerve [59]. HRV can be assessed by time domain, frequency domain, and nonlinear variables [60]. The standard deviation of the RR intervals (SDNN) is used as an overall estimate of autonomic function. The square root of the mean squared difference between the adjacent RR intervals (RMSSD) is predominantly influenced by vagal tone [61]. SDNN is an index of general health while RMSSD is an index linked to the cholinergic anti-inflammatory pathway (CAP) [62]. These parameters show robust circadian rhythmicity, and melatonin has been studied as a possible intervention to modulate the autonomic nervous system [63]. The published findings show that treatment with melatonin for 3 months (3 mg/day) induces an improvement in cardiac autonomic modulation in melatonin-non-proficient patients [64].

3.6. Melatonin for Autonomic Modulation: A Powerful Strategy for Militaries

A recent study examined the effects of melatonin (2 mg/day) administration on heart rate variability (HRV) in 26 healthy men. The findings indicate that melatonin administration increases cardiac vagal tone in the supine position in awake men. Melatonin administration also seems to exert suppressive effects on sympathetic tone [65]. This is extremely interesting data for the military, as low dosages of melatonin may be sufficient to supplement autonomic modulation and cardiovascular function. This is particularly significant as this molecule is extremely safe, even at very high doses. Taking melatonin in the evening facilitates an increase in vagal tone and, therefore, helps to create the physiological circadian response of the stress system (activating the parasympathetic system in the bathyphase to deactivate it adequately in the acrophase). Moreover, it facilitates an adequate psychophysical energy level to carry out the complex tasks that the military must deal with on a daily basis.

3.7. Melatonin to Improve Physical Endurance

Physical exercise, stimulating the sympathetic nervous system, can affect the secretion of melatonin. Melatonin is used as a natural supplement among athletes to regulate sleep cycles and protect muscles from oxidative damage due to the type and intensity of the activity performed. Exercise ≥ 50% VOmax2 induces an increase in ROS/RNS concentrations above physiological levels. The production of these harmful agents depends on various factors (e.g., determinants of exercise, postural position during exercise, training state, age, sex, and diet) [66]. Prolonged intense training also reduces an athlete’s endogenous melatonin level [67]. Based on published data, the optimal way for elite athletes to take melatonin (presumably equally applicable for military personnel) is at a dose of 10 mg in the evening to exploit its antioxidant properties, improve sleep quality, and enhance physical performance.

3.8. Melatonin to Improve the Physical Performance of Military Personnel

Large doses of melatonin taken alongside physical activity may hinder performance, primarily due to its effect on sleepiness and sympathetic depression [68]. However, in cases of sleep disturbance or jet lag syndrome, the combination of exogenous melatonin and outdoor physical exercise (to increase exposure to natural light) is a means to improve performance in sports. Thus, the same can be assumed for military combat personnel.

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