Melatonin and Health Benefits

This article is separated into 5 sections, each of which can be individually downloaded. It is a 'work in progress' incorporating new information whenever time permits.

Section 2

Depression to Obesity

1. Introduction; Age-related biological changes and increased life span; Alcohol-induced damage; asthma; autism; behaviour; bladder; blood-brain barrier; blood flow; blood pressure; brain damage; burns; cancer; cardiovascular support; Central Nervous System (CNS) injuries and diseases; chemical; dementia

2. Depression, bipolar disorder and mood control; diabetes, diabetic retinopathy; DNA damage; drug dependency; drug interaction; eye problems; fibromyalgia; headaches; head injury; height; immune system effects; infertility; inflammatory conditions; Irritable Bowel Syndrome (IBS) and other gastric problems; kidneys; learning and memory; light at night; light pollution; liver damage; lung injury; malaria; menopause; metabolic disorders; mitochondrial dysfunction; mouth diseases; nerve damage; neurocognitive functions; Neurodegenerative diseases, such as Huntington's disease; neurodevelopmental disorders; nitric oxide interaction; obesity

3. Operation trauma; ovarian disease; pain relief; pancreatitis; Parkinson's disease; plants; pregnancy and reproduction; radiation side effects; schizophrenia; sciatic nerve injury; scoliosis; skin effects; sleep, sleep apnoea; spinal cord injury; stress; stroke; testicular protection; thyroid; toxin protection; treatment side effect reduction; vaccinations; ventilator-induced lung injury; Wi-Fi

4. Melatonin suppressors: Alcohol; age; baby crying; cancer; chemicals; diet; weight; electromagnetic fields (EMFs), powerfrequency radiation; occupational radar exposure; radiofrequency radiation; light; light at night (LAN); light wavelength; smartphone; fracture risk

5. References – 467 references

Depression, bipolar disorder and mood control

Serotonin, from which melatonin is derived, is involved in mood control and changes in melatonin levels may be the mechanism underlying the links between EMFs and chronic fatigue, depression and suicide. Akpinar (2008) found that nocturnal melatonin levels of people with major depression and multiple sclerosis, were significantly lower than those with multiple sclerosis but without accompanying depression.

The occurrence of disturbed sleep is one of the principal diagnostic criteria for major depressive disorder (MDD). There is evidence of reciprocity between the two conditions such that, even in the absence of current depressive symptoms, disturbed sleep often predicts their development. It has been suggested that the recently introduced novel melatonin agonist has been very effective in improving the mood of depressed patients because of its ability to improve sleep quality. The use of melatonin is a promising treatment for depression (Rahman 2010, Pandi-Perumal 2009, Serfaty 2010). Agomelatine, a novel melatonergic antidepressant has been shown to improve sleep in depressed patients and to have an antidepressant efficacy that is partially attributed to its effects on sleep-regulating mechanisms (Srinivasan 2009).

A Turkish study (Ergün 2008) found that the co-administration of the antidepressant imipramine together with melatonin was better than either separately at ameliorating the symptoms of depression, depending on dosage, and there was no interaction between the drugs.

Rats chronically exposed to short daylight or to melatonin regimen mimicking short daylight, showed anxiety- and depression-like behaviours (Ashkenazy 2009). It is important that exposure to daylight is part of everyone's daily rhythm, especially people who work primarily in conditions of artificial light which has a different spectrum to that of natural daylight. An antidepressant drug structurally similar to melatonin, improved sleep without causing daytime sedation, sexual or cardiac adverse effects, weight gain or discontinuation syndromes (Dubovsky & Warren 2009).

Dallaspezia & Benedetti (2009) say *"Chronotherapeutic strategies based on controlled exposures to environmental stimuli that act on biological rhythms have shown good efficacy in the treatment of illness episodes".*

Melatonin improved concentration, focus & memory, but primarily reduced the levels of depression and anxiety (Arushanian 2012). The authors stated *"Shifts in the psychoemotional state were more pronounced than changes in the cognitive functions."*

Lewy (2009) in a recent review, also acknowledges that many, if not all, mood disturbances have a circadian misalignment component of the phase-delay type, which can be treated with bright light in the morning and/or low-dose melatonin in the evening.

Diabetes

An experiment by Gül (2008) found that the administration of melatonin reduced corneal injury in diabetic rats. Kedziora-Kornatowska (2009) found an improvement of antioxidative defense after melatonin supplementation in people with non-insulin dependent diabetes mellitus (NIDDM), and suggest melatonin supplementation as an additional treatment for the control of diabetic complications, especially in the elderly.

A diabetic woman, treated with phototherapy, which increased her melatonin secretion, required less insulin (Nieuwenhuis 2009).

A low dose of melatonin was found to be effective in reducing hepatic oxidative stress in diabetes (Shaker 2009, GG Korkmaz 2012).

The increase in free radical production and the inhibition of antioxidant activity in diabetes were both prevented by melatonin administration (Bicer 2012).

Agil (2013) found that oral melatonin administration improved the state of inflammation and oxidative stress which underlie the development of insulin resistance with its consequences – metabolic syndrome, diabetes and cardiovascular disease. Melatonin was found to help reduce insulin resistance in a study by Ghaisas (2011). Through modulation in T cell responses, Ren (2017) found that melatonin exerts beneficial effects in various inflammatory diseases, such as Type 1 diabetes, systemic lupus erythematosus and multiple sclerosis.

Diabetic retinopathy

Melatonin can stimulate cellular signalling pathways that are protective against retinal injury during diabetic retinopathy (Jiang 2012).

DNA damage

Melatonin prevents DNA damage (Tajes-Orduňa 2009).

Drug dependency

In an experiment on morphine-induced conditioned 'place preference' in mice, injected melatonin was found to reverse the effect (Han 2008).

Drug interaction

Kidney damage is a major complication of acetaminophen (APAP), a widely used analgesic and antipyretic drug. Ilbey (2009) found that administration of melatonin protected against APAP-induced kidney damage.

The effect of a cancer suppressor drug (Celecoxib) was enhanced when melatonin was given in combination (Orendas 2009).

People (in 9 European countries) were able to reduce consumption of benzodiazepines and similar drugs (with their associated adverse health effects) for the treatment of insomnia, confusion, cognitive impairment, Alzheimer's disease and cancer, when melatonin was available instead (Clay 2013).

Eye problems

In one study (Sande 2008), melatonin was found to prevent the clinical, biochemical, histological, ultrastructural and functional consequences of experimental uveitis (inflammation of the interior of the eye). Melatonin prevented and reversed the effect of ocular hypertension on retinal function, thus offering to be a promising resource in the management of glaucoma (Belforte 2010). Melatonin is able to relieve intraocular pressure (Musumeci 2013, Martínez-Águila 2013).

Oral melatonin premedication for patients undergoing undergoing cataract surgery under topical anesthesia was found by Ismail & Mowafi (2009) to provide anxiolytic effects, enhanced analgesia and decreased intraocular pressure resulting in good operating conditions.

Melatonin had a protective effect on retinal pigment cells against induced oxidative damage. The mechanism possibly involved reinforcing the cell viability, strengthening the activity of antioxidase, and reducing apoptosis (Xu 2009). In a study by Ozguner (2006) melatonin reduced retinal oxidative stress after long-term exposure to 900 MHz emitting mobile phone.

Melatonin protected against retinopathy in premature animals (Kaur 2013).

Melatonin supplementation seems to have protective effects on the oxidant system, following lens injury after WiFi exposure (Tök 2014).

Fibromyalgia

Fibromyalgia is a painful syndrome, that is experienced by many people as a precursor to ES. It has been suggested that melatonin supplementation may be effective in treating the pain associated with fibromyalgia, as well as addressing the sleep problems common in this syndrome (Reiter 2007).

Headaches

Melatonin was found to decrease the number of headaches suffered by children. In 14 out of 21 children headaches had reduced by 50% and 4 children had had no headaches at all after 3 months (Miano 2008).

Head injury

Melatonin was found to reduce brain oedema thus having a neuro-protective effect on secondary brain damage following head injury (Ismailoglu 2012).

Height

The height of Japanese adolescents was found to be inversely correlated with the distribution of day length at a light intensity greater than 4,000 lux (Yokoya 2012). Day length was thought to affect height by affecting the secretion of melatonin, which inhibits sexual and skeletal maturation, which induces increases in height. Exposure to light intensity greater than 4,000 lux appears to be the threshold at which light intensity begins to affect the melatonin secretion of people who spend much of their time indoors.

Immune system effects

While it is clear that melatonin interacts with the immune system (Arushanian 2002, Carrillo-Vico 2005), the details of those interactions are unclear, although a review by Carrillo-Vico (2013) concluded that melatonin was an immune buffer, acting as a stimulant under immunosuppressive conditions or as an anti-inflammatory compound in the presence of acute inflammation. Melatonin was found to be of high adaptive significance in wild animals for balancing the immunity when the body is immunocompromised by ecologically stressful conditions (Gupta & Haldar 2013).

There have been few trials designed to judge the effectiveness of melatonin in disease treatment. Most existing data are based on small, incomplete, clinical trials. Sirajudeen (2011) found improved immune responses and other cellular changes in chicks after melatonin was added to their water, though another study had found this was an age-dependent effect (Sharman 2008). Cardinali (2008) found that melatonin has the potential therapeutic value to enhance immune function in aged individuals.

Zhou (2009) found that melatonin promoted the proliferation of neonatal cord blood mononuclear cells and peripheral blood mononuclear cells and thus enhanced the lymphocyte immune system.

Sirajudeen's team felt that long-term rather than short-term administration of melatonin was more effective at reducing toxicity.

Cernysiov (2010) found that antibodies significantly decreased in mice exposed to light and daily melatonin treatment brought the antibody level back to normal.

Infertility

Serum and seminal plasma melatonin levels have been found to be significantly low in infertile males (Awad 2006).

Microwaves from mobile phones are one of the environmental toxicants that are capable of compromising male fertility by inducing oxidative stress and apoptosis in the testes. Melatonin exerts potent antioxidant effects in the testes of rats exposed to microwaves by decreasing the intensity of oxidative stress; it also reduces DNA fragmentation (Sokolovic 2015).

Inflammatory conditions

It has been suggested (Maldonado 2010) that melatonin could exert a regulatory effect on inflammatory conditions which are mediated by mast cells.

Kara (2013) found that when periodontitis was induced, melatonin reduced the oxidative damage in the rats' periodontal tissue by inhibiting the inflammatory effects and by restoring the antioxidants.

Kadena (2017) demonstrated that melatonin regulates inflammatory responses by inhibiting specific subsets of transcription factors (TFs) by disrupting actin dynamics in the macrophage.

Irritable Bowel Syndrome (IBS) and other gastric problems

The gastrointestinal tract secretes 400 times as much melatonin as the pineal gland (Bubenik 2008, Werbach 2008). In animal studies, it protects against gastrointestinal ulcerations, and is effective in treating functional dyspepsia and irritable bowel syndrome. According to Bubenik, laboratory and clinical studies indicate that the utilisation of melatonin can prevent or treat pathological conditions such as oesophageal and gastric ulcers, pancreatitis, colitis, IBS and colon cancer. In a study by Konturek (2008), removing tryptophan (a dietary precursor of melatonin) from the diet of rats delayed healing of gastric ulcers.

In a review by Zhernakova & Rybnikova (2008), the authors concluded that "*taking into account melatonin properties as well as the results of numerous experiments demonstrating its ulcer-protecting effects in different ulcer models, the role of disorder in the melatonin production in the occurrence and exacerbation of DU is undoubted. There are data on the participation of melatonin in the development and clinical course of such intestinal disease as various forms of colitis, irritated bowel syndrome, and*

'nighttime colics'. A direct association between melatonin and carcinogenesis in the alimentary tract has been demonstrated experimentally."

Melatonin significantly helped reduce cellular oxidative DNA damage in people with functional dyspepsia (Klupińska 2009).

Melatonin administration has been shown to protect against oesophageal lesions in animals.

Subjects with constipation predominant IBS secreted more melatonin than their healthy counterparts (Stepień 2009).

It was found that melatonin may be a promising candidate for the future research of agents that can modulate bowel motility and other IBS symptoms, in two studies by Lu (2005, 2009).

Gastric ulceration can be induced in rats by an administration of 15% hydrogen peroxide. Mohamadin (2009) found that the administration of melatonin 30 minutes before the hydrogen peroxide reduced the development of gastric lesions. The higher the dose, the greater the reduction.

Melatonin pretreatment significantly reduced haemorrhagic lesions and decreased oesophagal lipid peroxidation aggravated by Reflux Esophagitis (RE). Melatonin's free radical scavenging properties and antioxidant effects resulted in the improvement of oesophagal defence mechanisms (Lahiri 2009).

Oral melatonin was found to be promising for the treatment of gastro-oesophageal reflux disease (GERD) (Pereira 2006, Kandil 2010), also relieving epigastric pain and heartburn.

Melatonin was found to reduce gastric damage caused by treatment with NSAIDs (Maity 2009).

Pretreatment of jaundiced rats with melatonin protected against gastrointestinal ulceration (Moezi 2010).

Kidneys

Melatonin treatment had a protective effect on kidney damage induced in rats by 900 MHz phone radiation (simulating the sort of damage that can occur by attaching a mobile phone on standby to the belt) (Oktem 2005), or damage induced by radiation as a result of radiotherapy (Kucuktulu 2012). Ozguner (2005) found that melatonin prevented renal tubular injury by reducing oxidative stress and protected the kidney from oxidative damage induced by 900 MHz mobile phone.

Acute renal dysfunction is a frequent complication after cardiac surgery with cardiopulmonary bypass (CPB). Melatonin was effective in preventing CPB-induced renal damage (Wang Z 2009).

Melatonin also reduced the cortisol response to adrenocorticotropic hormone (ACTH), suggesting a direct melatonin action on the adrenal gland Campino (2008).

Donor preconditioning with melatonin protected kidney donor grafts from ischemia/reperfusion induced renal dysfunction and tubular injury (Li 2009).

Prenatal exposure of rat kidneys to 900 MHz EMF resulted in increased total kidney volume, and decreased the numbers of glomeruli (filtering units). Melatonin prevented adverse effects of EMFs (Ulubay 2014).

Learning and memory

the combination of physical exercise and melatonin may be an effective treatment for diseases affecting the hippocampus neurogenesis, involved in learning and memory functions (J Liu 2012).

Light at Night

The adverse effects of excessive use of artificial light at night (ALAN) are becoming increasingly evident and associated with several health problems including cancer. A putative mechanism of action involving epigenetic modifications mediated by pineal melatonin is discussed in relation to cancer prevalence (Haim & Zubidat 2015). Taking into account that ALAN-induced epigenetic modifications are reversible, early detection of cancer development is of great significance in the treatment of the disease.

Reduced melatonin at night is a potential physiological mechanism underlying the advanced onset of morning activity of urbanised birds (Dominoni 2013). Based on the pattern of melatonin secretion, the authors suggest that European blackbirds responded to light-at-night as if they were exposed to a longer day than birds kept under dark nights.

Light pollution

The International Agency for Research on Cancer (IARC) has ruled that *"shift-work that involves circadian disruption is probably carcinogenic to humans"* (Group 2A). Light-at-night disrupts the circadian rhythm and suppresses nocturnal production of melatonin. Constant light was found to accelerate age-related switch-off of the oestrous function (in female rats), induced the development of metabolic syndrome and spontaneous tumour development, and shortened the life span in both male and female rats. Melatonin given in nocturnal drinking water prevented the adverse effects of constant light (Anisimov 2012).

Liver damage

The rhythm of melatonin secretion and its blood level changes in cirrhotic patients. The elevated melatonin blood levels both at night and day may account for some of the clinical manifestations of hepatic encephalopathy (Chojnacki 2013).

Melatonin was found to protect against damage to the liver induced by interrupted blood flow (Li 2008), by carbon tetrachloride in rats (Hong 2009), and acetaminophen overdose (Liang 2012). It was also found to protect against burn-induced liver damage (Bekyarova 2012). Melatonin reduces liver damage by decreasing oxidative stress (Aktas 2014, Kireev 2013). Melatonin also reduced oxidative stress and inflammation in the liver due to aging (Kireev 2008).

A high dose of melatonin was found to have an antiproliferative effect on hepatoma cells (Ozdemir 2009). Used together with Doxorubicin, hepatoma cell growth was inhibited and the combination induced cell apoptosis (Fan 2010).

Melatonin reduced apoptosis and necrosis in severe acute pancreatitis (Ni 2008).

Lung injury

Melatonin possesses a protective effect on lung tissues during acute lung injury (Yip 2013) through scavenging free radicals (Pan 2009) and inhibiting the activation of nuclear factor-

KappaB (Zhang 2008). Melatonin also protected from lung injury after pancreatitis was induced in experimental rats (Huai 2012).

A study by Jang (2013) found that melatonin reduces radiation-induced lung injury through the reduction of oxidative stress which increased following lung irradiation.

Malaria

Melatonin has been found to have a two-pronged effect on malaria development. Firstly melatonin agonists can prevent the maturation of the parasites responsible for malaria, and melatonin administration at high dosages can be used to inhibit apoptosis and liver damage resulting from the oxidative stress in malaria (Srinivasan 2010).

Menopause

Oxidative stress has been proposed to explain the biological side effects of experimental menopause. Melatonin prevented Oxidative stress in ovariectomized rats (Dilek 2010).

Metabolic disorders

The melatonin effect mediated by haemoglobin-oxygen affinity change may be used for the correction of metabolic disorders and the improvement of the body's resistance to low environmental temperature (Hlutkin & Zinchuk 2008).

Mitochondrial dysfunction

Mitochondrial dysfunction is one of the main causative factors in a wide variety of complications such as neurodegenerative disorders, ischemia/reperfusion, aging process, and septic shock. Melatonin, the pineal gland hormone, is selectively taken up by mitochondria and acts as a powerful antioxidant, regulating the mitochondrial bioenergetic function (Sharafati-Chaleshtori 2017). The high levels of melatonin produced by mitochondria and chloroplasts are used to protect these important cellular organelles against oxidative stress and preserve their physiological functions (Tan 2013). The superior beneficial effects of melatonin in both mitochondria and chloroplasts have been frequently reported.

Mouth diseases

Melatonin, which is released into the saliva, may play a role in protecting the oral cavity (periodontal diseases, herpes viral infections and Candida, oral ulcers and oral cancer) from tissue damage caused by oxidative stress (Gómez-Moreno 2010, Srinath 2010). Melatonin levels were low in diseased periodontal tissues, and lowest in the aggressive periodontitis group (Almughrabi 2013).

Nerve damage

Melatonin was found to offer significant protection against nerve damage in a study of induced sciatica in rats (Daglioglu 2009).

Neurocognitive functions

In a review of studies, melatonin has been found to maintain neurocognitive functions after irradiation (Manda 2009).

Neurodegenerative diseases, such as Huntington's disease

Results of the study by Tasset (2009) supported the hypothesis that melatonin could be useful in the treatment of diseases such as Huntington's disease, possibly by reducing oxidative stress.

Ali & Kim (2015) concluded that melatonin could be an effective, promising, and safe neuroprotective candidate for the treatment of progressive neurodegenerative disorders, such as Alzheimer's disease.

Melatonin has a role in mitochondrial protection, which could prevent development and progression of neurodegeneration. Since the mitochondrial dysfunction is a primary event in neurodegeneration, the neuroprotection afforded by melatonin is thereby more effective in early stages of the diseases (Wongprayoon & Govitrapong 2017).

Neurodevelopmental Disorders

Children with neurodevelopmental problems who did not fall asleep within an hour of lights out, or who had less than 6 hours of continuous sleep were helped by the administration of melatonin, which increased sleep time on average by 23 minutes and fell asleep quicker by a mean of 45 minutes (Appleton 2012). In a study by Gringras (2012) children with developmental disorders fell asleep quicker with melatonin supplementation, but woke earlier, thus not extending their sleep period.

There was no degradation in melatonin when it was mixed with soft food or liquids for administration. It was stable for up to 6 hours at room temperature (Shah 2008).

Nitric oxide interaction

Yariktas (2005) found that exposure to a 900 MHz source increased nitric oxide (NO) levels in the sinus and nasal mucosa. They suggested that increased NO levels may act as a defence mechanism and relate to tissue damage. Melatonin seemed to have a beneficial effect preventing the changes in the mucosa.

Obesity

Short sleep duration is associated with obesity, and urinary 6-sulfatoxymelatonin (6-OHMS), the principal metabolite of melatonin, is closely related with sleep. However, a study by J Lee (2012) did not find that melatonin production was reduced consistently in obese girls.