Melatonin's protection against cancer

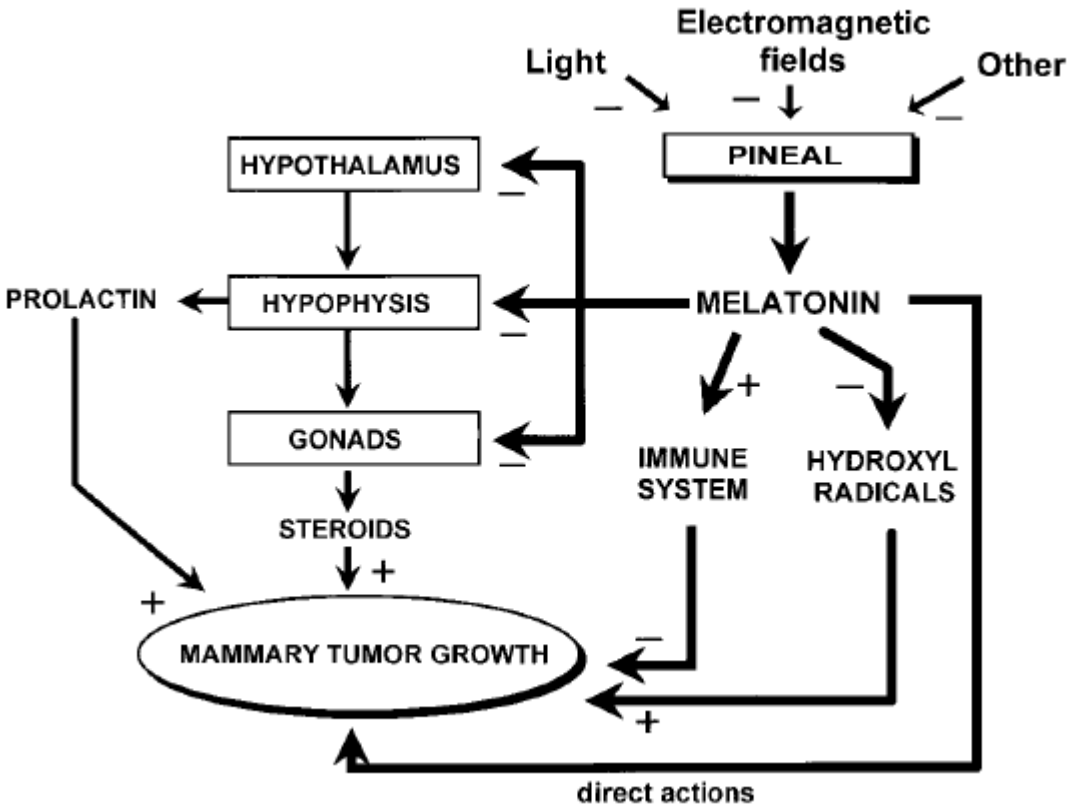

Figure 1. Diagram showing the possible ways through which the pineal gland could influence mammary carcinogenesis (24).

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Summary

Melatonin the primary hormone of the pineal gland appears to be one of the most important and multifunctional hormones. In this bachelor thesis the possible ways of how melatonin protects against cancer were reviewed. Most research of melatonin's protective function against cancer is done in breast cancer cells. Therefore a further question addressed here is "why and how does melatonin protect against hormonal cancers?"
Melatonin influences cancer cells in several ways. It has an immunomodulatory action on the immune system and can protect the bone marrow during chemotherapy. Melatonin has a protective function against free radical damage by working as one of the most efficient antioxidants of the body. As an antioxidant melatonin inhibits inducible nitric oxide synthase, scavenges peroxinitrite, detoxifies free radicals and supports superoxide dismutase. These effects and because melatonin has no prooxidative actions make melatonin better then any of the classical antioxidants in protecting against cell damage and by this way protecting against cancer.
Melatonin has an antiproliferative effect in cancer cells by affecting the cell cycle. Two ways in which melatonin affects the cell cycle might be via the up regulation of the tumor suppressor gene p 53 and by working as a calmodulin antagonist. Furthermore melatonin might protect against cancer by keeping the gap junctions intact and melatonin can inhibit the growth of tumor cells by inhibiting linoleic acid uptake. In addition melatonin can influence the sex hormones. Melatonin may suppress the estrogen response pathway in breast cancer cells by modulation of the synthesis of estradiol induced growth factors and by altering their capacity to act on their cellular targets.
Concluding, although melatonin seems to be able to affect cancer cells in many ways the mechanisms by which melatonin may be protective against cancer are not completely understood and proven but need more research.

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Introduction:

Melatonin is the primary hormone of the pineal gland. It is synthesised from trypthophan. Trypthophan is converted to serotonin and then metabolized to melatonin by hydroxindole-O-methyltransferase (HIOMT) (figure 2). The synthesis and release of melatonin reaches a peak in the dark at night. This peak also occurs at night in nocturnal animals like rats. The secretion and synthesis of melatonin by the pineal gland during the night results from the rhythmic neuronal activity generated by the suprachiasmatic nuclei (SCN). The SCN is entrained to the light dark cycle. Exposure to light at night interferes with the 24 hour cycle and rapidly suppresses the melatonin production (1). Although the pineal gland and its hormone melatonin were discovered relatively late, melatonin now appears to be one of the most important and multifunctional hormones. It is mostly used as a sleep drug or to avoid jet lag. But research is giving more and more credit to melatonin in a big array of functions. Melatonin has been proven to affect the immune system (2 & 3), for example by enhancing the immune system in situations of stress. Melatonin has a protective function against free radical damage by working as one of the most efficient antioxidants of the body (4). In this way melatonin can protect cell membranes, proteins and the DNA. This might be an important aspect in the fight against cancer. Except for melatonin's function as an antioxidant and its enhancing effect on the immune system there is research piling up that melatonin might have a lot more ways in which it can protect against cancer. In this bachelor thesis the possible ways of how melatonin protects against cancer will be reviewed. There is some indication that the anti cancer effect of melatonin has something to do with the sex hormones (5, 6, 7). Most research of melatonin's protective function against cancer is done in breast cancer cells. So a further question that will be addressed here is "why and how does melatonin protect against hormonal cancers?" Research on this question might be of special importance to people working in night shifts. Especially women working in shift work seem to have a greater risk of breast cancer (8). The hypothesis that the suppression of melatonin by exposure to light at its peak time in the night plays a role in the increased risk of getting breast cancer is appealing but needs further proof.

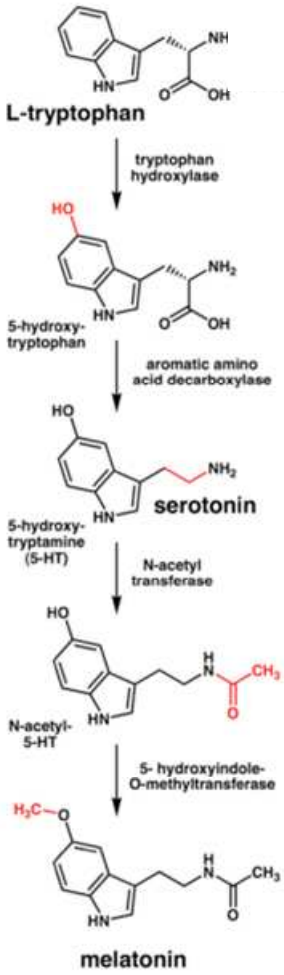

Figure 2. Metabolism of tryptophan into serotonin and melatonin (9)

Melatonin as an antioxidant:

The first living organisms on earth billions of years ago were one celled organisms which were anaerobic. At this time there was almost no oxygen in the air. These first cells produced oxygen as a waste product. Eventually this oxygen killed the anaerobic organisms and gave way to aerobic organisms. Nowadays the air consists out of 21 % oxygen. But even for aerobic creatures oxygen had a downside. The processes which involve oxygen produce free radicals. These free radicals can change molecules, perforate cell membranes and damage DNA (4). In order to survive, aerobic organisms had to find mechanisms to protect or repair this damage. One of the mechanisms of protection came in the form of antioxidants. Melatonin as an antioxidant appears to have been one of the first molecules to do this job. This made melatonin essential for life which can be seen by the fact that all life forms have melatonin. Later in more complex organisms melatonin evolved over billions of years to function as a hormone. Currently it is known as an antioxidant (10) and a master hormone.

Free radicals are different from other molecules in that they have an unpaired electron in their outer orbit. This makes the molecule unstable and willing to steal an electron. Electrons are the glue that holds molecules together. So by stealing an electron the free radical interferes with other molecules deforming or destroying it. In this way it can corrupt the genetic code leading to disease or death.

The DNA strand is a big molecule with a lot of surface area where it is vulnerable to free radical damage. Most of this damage is almost immediately repaired before the cell divides. But at least one out of the trillion times the damage goes unrepaired resulting in a mutant cell. This can seed a malignant tumor. Melatonin protects the DNA from cancer inducing toxic substances (11). Even very small amounts of melatonin protect the DNA. In a study of Dun-Xian Tan et al 1993 they found that in rats 0.2 mg/kg melatonin was already enough to protect the DNA against 300 mg/kg of the carcinogen safrole (11).

The antioxidants that are most often used as interventions to counteract damage by free radicals are vitamin A, vitamin C and vitamin E. However, those antioxidants sometimes fail in giving protection against oxidative stress. In a review article of Ahmet Korkmaz et al 2009 a theoretical explanation for this failing was described (10). This explanation states that the way oxidative stress works is much more complex than previously thought. This complexity involves nitric oxide (NO) and the nitric oxide synthase (NOS) family. NO can bind with the superoxide anion radical (O2-) and so form peroxynitrite (ONOO-). ONOO- has a direct toxic effect that leads to lipid peroxidation, protein oxidation and DNA damage (12). In addition ONOO- has a positive feedback cycle by which it inhibits the antioxidants that normally keeps the ONOO- production in check (10). Normally the enzymatic antioxidant superoxide dismutases (SOD) prevent the formation of ONOO- by degrading O2- to H2O. But when there is a lot of NO it reacts so fast with oxygen that the normal antioxidants can not successfully compete with NO for O2- (13). A high level of NO can happen by an increase in the production of reactive oxygen species. The production of reactive oxygen species reduces the amount of NO that comes from endothelial NOS (eNOS) and activates inducible NOS (iNOS). iNOS can cause a NO production that is a 1000 times bigger than what is produced by eNOS under normal physiological circumstances. This means that the free radicals from oxygen are only the first step in the mechanism of DNA and cell damage that can lead to cancer. The combination of higher NO levels, more O2- and the formation of high levels of ONOO- is called the “devil’s triangle” (figure 3) (10).

Where the normally used antioxidants fail to fight this devil's triangle melatonin might be the answer. Melatonin with its many functions has iNOS inhibitory and ONOO- scavenging properties (14). Also some of melatonin's metabolites can detoxify free radicals (15) and melatonin supports several enzymatic antioxidant enzymes such as SOD (2). It influences not only the activity of SOD but also the mRNA levels under normal conditions and during elevated oxidative stress (2).

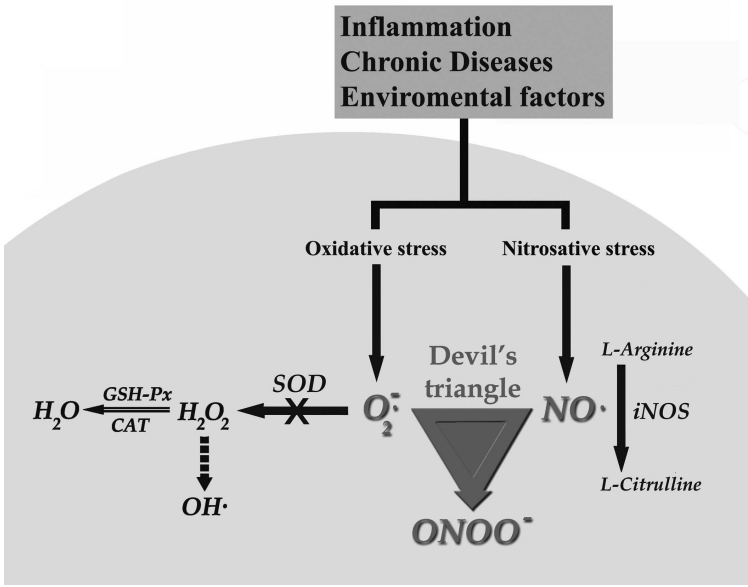

Figure 3. The devil's triangle. Inflammation, chronic diseases and environmental factors like radiation create a lot of O2- and NO production. Under normal conditions SOD degrades O2- to H2O. But in the case of NO from iNOS ONOO- will be formed which reduces the amount of O2- that is degraded by SOD (10).

Except for being the solution to the devil's triangle melatonin has another advantage over the classical antioxidants. This is that it has no prooxidative actions. The classical antioxidants work by donating an electron to neutralize a free radical. By donating this electron they are transformed into an oxidized state. Then antioxidants like vitamin C and vitamin E will recycle to their old form at the expense of glutathione (GSH). Glutathione however is also an antioxidant and is an even better antioxidant than vitamin C or vitamin E (10). Melatonin does not recycle but sacrifices itself after scavenging free radicals. Therefore it does not use GSH but sometimes even increases the GSH levels. In a study of Carlo Pieri et al 1994 (16) melatonin was compared with the antioxidants vitamin E, vitamin C and GSH. They used a method based on the loss of fluorescence exhibited by the protein beta-phycoerythrin when oxidized by oxygen radicals. Under constant production of free radicals they found that melatonin was two times more active than vitamin E which was believed to be the most effective lipophilic antioxidant. Melatonin was also a little less than two times more active than vitamin C and three times more active than GSH. So by being the best antioxidant of the body melatonin might protect against the development of cancer by protecting against free radical damage to the cell membrane and the DNA.

The pathologies of aging may also be the result of free radical damage. The free radical theory states that free radical damage gets less repaired over time due to a diminishing amount of antioxidants. Which results in gradual erosion so that malignant cells can develop. A missing link in this theory was that a loss of antioxidants over time was not proven. Most antioxidants don't diminish over time. But recent studies found evidence that melatonin does diminish over time (17). This however remains some what uncertain since contradictory results have been reported in healthy aging subjects (18). In a review article of Reiter 1995, he gives a summary of theories of how melatonin could work as an anti aging factor. One theory proposes that aging and aging related diseases come from the desynchronization in the body because of a loss of melatonin. Reiter also gives a theory why the melatonin levels decrease by aging. This might be due to a decreased number of receptors on the pinealocyte membrane or a destruction of neurons in the SCN (17).

Melatonin and the immune system:

Immune cells produce free radicals as a weapon against for example cancer cells (19). However by overproduction during for example a serious viral invasion this weapon will also damage healthy cells which can lead to cancer. Melatonin can protect against this by acting as an antioxidant. But except for its function as an antioxidant melatonin also seems to be able to affect the immune system. Melatonin has an immunomodulatory action on the immune system while under the inhibiting effect of stress (19). Georges J.M. Maestroni et al 1986 showed that melatonin counteracts the immunosuppression by corticosterone that was given to rats in drinking water (19 & 20). Testosterone also has an inhibitory effect on the immune system. Is has proapoptotic effects and reduces macrophage proliferation (21).

Melatonin also protects the bone marrow which normally gets damaged by chemotherapy (22). Georges J. M. Maestroni et al 1994 implanted rats with lung cancer cells and gave them cancer therapy drugs and melatonin. They found that melatonin can protect the bone marrow without interfering with the anticancer action of chemotherapy drugs. The precise mechanism by which melatonin protects the bone marrow is still unknown but T helper cells seem to play a role. Melatonin can also stimulate the growth of bone marrow cells. The bone marrow is the place where white and red blood cells are produced. Chemotherapy results in a great loss of white blood cells. Bone marrow stimulation by melatonin can help replenish their numbers. Melatonin couples to T helper cells. T helper cells stimulate production of an IL 4 like factor. This stimulates production of the granulocyte macrophage colony stimulating factor (GM CSF). GM CSF stimulates stem cell growth in the bone marrow. Giving GM CSF is rather expensive and has side effects. Melatonin is not expensive, has no side effects and might be as effective. By coupling to T helper cells melatonin also stimulates natural killer cells which specialize in attacking cancer cells and virus infected cells (22).

Melatonin's effect on cell cycle:

Melatonin has an antiproliferative effect in cancer cells. It brings cells from a proliferative state into a differentiated state. Melatonin does this by inhibiting the progress of a cell through the cell cycle (23). The cell cycle consists of the S phase, M phase and the G0, G1 and G2 phases. In the S phase the DNA is replicated and in the M phase the cell undergoes mitosis. The G phases lie in between the S and M phase. The G0 phase is the resting state. A cell in this phase is differentiated and does not divide. When a cell leaves this resting state it enters the G1 state. Here RNA and proteins are synthesised. In this state the cell goes past checkpoint R, the restriction point. If it passes this checkpoint it will undergo DNA replication in the S phase. Melatonin works at this checkpoint in the cell cycle. It inhibits cells going through the restriction point and thereby prolongs their cell cycle by about 15% (23). When the cells then pile up in the G0 and G1 phase melatonin also affects cells that have progressed to the S phase by suppressing DNA synthesis (24).

A way in which melatonin inhibits the transition of a cell from G1 to the S phase may be by up regulating the tumor suppressor gene p53 (24). P53 activates a group of genes that are involved in apoptosis, for example p21/Waf1. In breast cancer cells this inhibits proteins in the G1 phase called G1 D type cyclins. These proteins are needed for a cell to go through the R checkpoint. So inhibition of this protein results in a cell cycle delay.

This cell cycle delay is of particular interest in breast cancer. The terminal ductal lobular units in human mammary glands are the most undifferentiated

structures of the developing ductal system and have a high risk of tumor initiation. This is due to the high proliferative rate of epithelium. Treatment with melatonin results in more differentiated cells that no longer proliferate in the ductal system and hereby makes it more resistant to cancer initiation (24).

Calmodulin is a calcium binding protein that has an important stimulating role in the proliferation of normal and neoplastic cells by working on processes like cell cycle progression and cytoskeletal integrity (5). Calmodulin is involved in the initiation of the S phase, initiation and completion of the M phase and cell cycle related gene expression. Also calmodulin concentrations affect progression through the G0/G1 phase and mitosis. It is necessary for re-entering cells from G0 back into the cell cycle and for overcoming the G1/S and G2/M boundaries. On top of all that, progression through the cell cycle involves enlargement and depolymerisation of microtobules and this is stimulated by calmodulin. Calmodulin antagonists have the opposite effects (5). Melatonin can bind calmodulin and induce changes in intracellular distribution of calmodulin from the cytosol to the cytoskeletal membrane. In this way melatonin has an antiproliferative effect. As a calmodulin antagonist melatonin inhibits DNA synthesis and blocks re-entry of cells into the cell cycle and mitosis (23).

Gap Junctions:

A finding that fits with the hypothesis that melatonin brings cells into a differentiated state is the breakdown of gap junctions in cancer cells. Healthy normal cells are in communication with each other by gap junctions. These gap junctions pass critical regulatory information between differentiated, non proliferating cells. Gap junctions can buffer against chemicals like pesticides by distributing the chemical over a lot of cells thereby diluting the chemical. And via gap junctions healthy cells can help neighbour cells that are sick or deprived. As long as the gap junctions intercellular contact stays intact the cell can get assistance from healthy neighbour cells (25). Communication between local cells is promoted by adhesion molecules like E-cadherin. A loss of E-cadherin expression correlates with a loss of gap junction intercellular communication. In cancer cells intercellular communication breaks down because of defective cell adhesion and malfunctioning gap junctional contacts (25). Factors that promote tumor growth down regulate gap junctional function and factors that have an anti-tumor effect up regulate and maintain intercellular gap junctional communication. Melatonin has this anti-tumor effect. The invasiveness of tumor cells also depends on cell surface adhesion molecules that are needed for cell-cell interactions. Low E-cadherin was found to be correlated with invasiveness (26). Melatonin increases the expression of E-cadherin (6) and thereby reduces the invasiveness of the breast cancer cells. By doing this it shifts the balance between differentiated cells and proliferative cells to more differentiated cells.

Melatonin and linoleic acid:

In a study of Robert T Dauchy et al 2007 (27) the inhibitory effect of melatonin on tumor cell growth was investigated. In previous studies (28 & 29) it was found that a metabolite of linoleic acid, namely 13-hypdroxyoctadecadienoic acid (13-HODE), stimulates the growth of cancer cells. The higher the fat percentage in the diet of rats was in these studies the higher the rate of tumor growth was. This growth stimulating effect in various cancer types under which breast cancer is suppressed by melatonin (28). To find out the underlying mechanism Robert T Dauchy et al 2007 perfused

tumors with blood that did not contain melatonin and blood that did. Their hypothesis was that melatonin would inhibit cAMP levels in the tumor which leads to a decrease in fatty acids uptake and suppression of linoleic acid metabolism to 13-HODE. And that these inhibitions would be reversed by a melatonin antagonist. They found that tumor cells perfused with melatonin reduced the cAMP levels by more than 75%. It inhibited linoleic acid uptake and 13-HODE production. And they also found that the inhibitory effect of melatonin was completely reversed by giving a melatonin antagonist. This proves that the mechanism by which melatonin inhibits tumor growth is a melatonin receptor mediated process.
Three membrane receptors have been found for melatonin, MT1, MT2 and MT3. The MT1 and MT2 receptors were found in mammalian tissues. These receptors are all G-protein coupled receptors. MT1 is coupled to a G-inhibitory protein so it inhibits the production of cAMP. The MT2 receptor is coupled to a Gq protein which works via phospholipase C (30).

Melatonin and sex hormones:

Melatonin has a counteractive role in the development of breast cancer cells via different pathways. Melatonin has direct actions on breast cancer cells which are anti proliferative and anti invasive (24 & 6). These direct actions have been mostly studied in MCF-7 human breast cancer cells. These breast cancer cells have estrogen and progesterone receptors. Estrogens play an important role in promoting the proliferation of breast cancer cells (31).
Melatonin inhibits the mitogenic effect of estradiol (E2) on MCF-7 cells and melatonin down regulates the expression of the estrogenreceptor (ER) by suppressing the transcription of the estrogenreceptor gene. Melatonin does this by an indirect mechanism and not by competing with estradiol for the hormone binding domain of the estrogenreceptor (23).

The estrogen receptor binds to estrogen responsive elements (EREs) in the DNA which makes genes become activated for transcription and makes them produce mRNAs and proteins involved in cell proliferation. When estradiol is absent the inactive receptor makes a complex with a variety of proteins that makes it unable to interact with EREs. When estradiol is present the receptor can bind to coactivators and begin transcription of the target genes. Estradiol can induce phosporylation of the amino terminal and ligand binding domains of the estrogen receptor and hereby increase the estrogen receptors binding to ERE and so promote transcription. Melatonin can block the ability of estradiol to stimulate the binding of the estrogen receptor with ERE (32). It probably does this by activating phosphatises or inhibiting phosphorylases but not by destabilizing the E2-ER-ERE complex through inhibition of estradiol induced phosphorylation (33).

Estradiol may induce proliferation of breast cancer cells by induction of growth factors such as TGFalfa and prolactin and by inhibiting the growth inhibitory factors like TGFbeta. Melatonin inhibits the expression of TGFalfa and also stimulates the expression of TGFbeta in breast cancer cells. In addition to this melatonin also blocks or reduces the mitogenic effect of both prolactin and epidermal growth factor (EGF) which has about the same structure and function as TGFalfa (24).
Thus melatonin may suppress the estrogen response pathway in breast cancer cells by modulation of the synthesis of estradiol induced growth factors and by altering their capacity to act on their cellular targets (24).

Tamoxifen inhibits the growth of breast cancer cells and is used as a treatment. Tamoxifen does this by acting on the estrogen receptor. Research of Sean T. Wilson et al 1992 shows that there is a hundred times better working of tamoxifen when the cells had a pre-treatment with melatonin (27). Also if melatonin is present with estradiol in the blood serum than it reversibly inhibits cell proliferation, reduces the metastatic capacity of cancer cells and counteract the stimulation by estradiol on cancer cell invasiveness (6).

Melatonin suppressed by light at night:

In most studies the antiproliferative effect that melatonin has on cancer cells was studied under constant levels of melatonin. Melatonin secretion in the body however is rhythmic with a 24 hour period (1). Cos et al 1994 (35) exposed breast cancer cells to either constant levels of melatonin or to a simulated diurnal rhythm of melatonin. They used groups with various levels of melatonin concentrations. They found that alternating concentration of melatonin over 24 hours that mimic the melatonin level in the normal physiological range has the largest antiproliferative effect on breast cancer cells (35). These are concentrations between 1 nM and 10 pM (24).

Humans spend about one third of their life sleeping. Before the invention of artificial light most of this sleep occurred during the night (36). Therefore the human body has evolved so that oscillations in our physiology, metabolism and behaviour are synchronized to the sun. This evolved under the conditions of bright sunlight during the day and complete darkness during the night. In our current society people in industrialized countries stay a lot indoors during the day and spend a lot of time in artificial light during the night time. This may obviously have consequences for the biological clock and its main signal, melatonin. Bright light at night almost immediately turns of melatonin production. This might be a part of the explanation why breast cancer is up to five times higher in industrialized countries (36). The western nations have become more and more a 24 hour society where a lot op people are exposed to artificial light at night at work and at home.

Women working in shiftwork may have an increased risk of cancer because of melatonin suppression by light at night (1 & 37). A research from Blask et al 2005 gives evidence for this statement. They perfused breast cancer cells with either melatonin deficient blood collected in the daytime or with melatonin deficient blood collected in the night time after exposure to 90 minutes of bright light or melatonin rich blood collected at night. They found that only tumors perfused with melatonin rich blood showed inhibited proliferation. The bright light at night apparently suppressed melatonin so far as to become the same level as in daytime blood.

Discussion:

Melatonin with its great variety of functions affects cancer development and growth via different pathways. As an antioxidant melatonin seems to be unique in its ability to affect the "devil's triangle" on every step. Melatonin inhibits iNOS, scavenges ONOO- (14), detoxifies free radicals (15) and supports SOD (2). This and because melatonin has no prooxidative actions makes it better then any of the classical antioxidants in protecting against cell damage and by this way protecting against cancer. Free radical damage is often pointed out as the cause of aging. So maybe the suppression of melatonin, the body's best antioxidant, by bright light that people who work in night shifts are exposed to stimulates aging and thereby aging related diseases like cancer.

A second pathway by which melatonin affects cancer is boosting the immune system (19). Melatonin has immunomodualtory effects on the immune system while under the inhibiting effect of corticosterone. Testosteron also inhibits the immune system (21). Maybe melatonin works by a similar mechanism when the immune system is inhibited by hormones like testosterone as when the immune system is inhibited by corticosterone. If this is true it may explain why melatonin is highly effective against hormonal cancers. An alternative explanation could be that while the immune system is suppressed by testosterone melatonin is not inhibited and thereby the only antioxidant left.

Melatonin also seems to have an effect on the cell cycle. The specifics of how this works are yet to be found. Two ways in which melatonin affects the cell cycle might be via the up regulation of the tumor suppressor gene p 53 (24) and by working as a calmodulin antagonist (32). Melatonin brings cells from a proliferative state to a differentiated state which inhibits cancer proliferation and cancer initiation. This may be of particular importance in breast cancer as the terminal ductal lobular units in the mammary gland are much undifferentiated and therefore have a high risk of cancer initiation. Evidence that corresponds with this differentiating effect is that melatonin up regulates and maintains gap junctions which are broken down in cancer cells (25). Another way by which melatonin might protect against cancer is by inhibiting the uptake of linoleic acid. A study of Robert Dauchy et al 2007 showed that this might work by a melatonin receptor mediated process. How the melatonin receptors work precisely is yet to be discovered.

Melatonin seems to be of special protection against hormonal cancer. A similarity between breast cancer and prostate cancer is that they are both initially hormone dependent. Breast cancer is stimulated by estrogen and prolactin and prostate cancer by testosterone. This similarity may be the reason why melatonin affects these two cancers. In breast cancer melatonin inhibits the effect of estradiol and down regulates the estrogenreceptor (23). The inhibitory effect of melatonin on the estrogen activation of the estrogen receptor is blocked by pertussin toxin. Pertussin toxin is a Gi-protein inhibitor. So this indicates that melatonin may work as an antagonist on the estrogenrepsons via the Gi-protein coupled MT1 receptor.

That melatonin has some protective functions specific against breast cancer might explain why women in shift work have a higher risk of breast cancer. Working in light at night suppresses melatonin. During menopause women have low melatonin levels (38), in men of this age this is almost not seen. Maybe this makes women more vulnerable to an absence of melatonin at a younger age. This might be a reason why night shift gives a higher risk of breast cancer but not so much prostate cancer.

Another explanation for the higher occurrence of breast cancer in the recent years could be the almost constant exposure to electromagnetic fields (EMFs). EMFs

seem to decrease the nocturnal melatonin levels (39). EMFs are all around us and extra exposure at night time may explain the higher incidence of breast cancer in night shift workers.

Another speculative theory why humans have a high incidence of breast cancer may be because we are no longer seasonal breeders. The duration of melatonin secretion at night by the pineal gland tells animals what time of year it is and influences their productive hormones (40). Humans stay a lot indoors and are not exposed to this clue. What may result in no seasonal inhibition of estrogen by melatonin and in this way a higher risk of breast cancer induced by relative more exposure to estrogen. This seasonal theory might also be relevant in men. Hamster's testes shrivel in the winter due to melatonin. Humans are no longer seasonal. Maybe melatonin in humans also has some sort of chastity effect. And therefore by inhibiting testosterone it will inhibit prostate cancer.

Concluding, although melatonin seems to be able to effect cancer cells in many ways the mechanisms by which melatonin may be protective against cancer and the questions whether low melatonin levels are of causal importance for development and growth of cancer cells are not completely understood and proven. More research is needed, but the existing data look promising and may eventually result in the advice to try to keep a 24 hour rhythm of endogenous melatonin levels intact as much as possible during a persons lifetime.

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