MOLECULAR CARCINOGENESIS 21:149–155 (1998)

WORKING HYPOTHESIS

Melatonin: Receptor-Mediated Events That May Affect Breast and Other Steroid Hormone–Dependent Cancers

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Epidemiological studies have suggested a possible link between extremely low frequency electromagnetic fields (EMFs) and increased rates of certain cancers. One cancer that has been postulated to be associated with EMF exposure is breast cancer, for which increased rates have been reported among electricians. These cancer associations are weak, and the link to EMF exposures remains tenuous. Understanding the mechanisms by which EMFs could have biological effects will help in elucidating the risk, if any, from EMFs. One hypothesis that has received considerable attention involves reduction of melatonin levels by EMFs. This hypothesis suggests that loss of melatonin affects a variety of hormonal processes such as estrogen homeostasis and thereby may increase breast cancer rates. Since this theory was first presented, putative melatonin receptors have been cloned, providing new tools with which to examine melatonin's mechanism of action and the melatonin hypothesis. These receptors are found in nuclear and membrane fractions of cells. The nuclear receptors (retinoid Z receptors) are found both in the brain and in non-neural tissues, whereas the membrane-bound receptors are found primarily in neural tissue and have a higher affinity for melatonin. These receptors may control a variety of hormonal and immunological functions, including the release of gonadotropins from the hypothalamus and pituitary and 5-lipoxygenase activity in B lymphocytes. This Working Hypothesis briefly reviews our current knowledge of melatonin receptors and then provides theories on how the inactivation of melatonin receptors may cause cancer and suggests areas of research for addressing this question. *Mol. Carcinog. 21:149–155, 1998.*

Key words: electromagnetic fields; light at night; estrogen; proliferation

INTRODUCTION

Some epidemiological studies have suggested that extremely low frequency electromagnetic fields (EMFs) may cause cancer in humans [1–4]. Most epidemiological studies have demonstrated a correlation between wire coding and childhood leukemia or brain cancer [1–3]. However, more recent studies have shown correlations between EMFs and breast cancer [4], although the association has been criticized and the mechanism of action has remained elusive [5,6]. A hypothesis proposed by Stevens et al. [7,8] suggested that light at night or EMFs may cause a reduction in melatonin production from the pineal gland. This in turn induces a number of biological effects, including increased estradiol release and possibly enhanced estrogen receptor levels, resulting in an increase in breast cell proliferation and subsequently breast cancers.

Although much current research and interest have focused on EMFs and whether they reduce melatonin concentrations, light at night may be a more likely cause of effects on melatonin and subsequent perturbations in hormone homeostasis. In just the past 100 yr, the lights used at night for reading, watching television, eating, and other activities have allowed us to change our schedules and have significantly increased our exposure to light after sundown. If the loss of melatonin due to electricity in modern industrial societies causes an increase in cancer, then light at night may be as likely a culprit as exposure to EMFs.

The purpose of this review is to explore mechanisms by which EMF- or light at night–induced loss of melatonin could affect hormone homeostasis and cause breast and other steroid hormone–dependent cancers. When the melatonin hypothesis was first presented, no putative melatonin receptors were known. The cloning of melatonin receptors has provided us with tools to understand melatonin and its biochemical actions. These tools can be used to increase our understanding of the mechanism of melatonin action and to examine the possible risk associated with a decrease in melatonin. The antioxidant properties of melatonin are another possible mechanism for inhibiting hormone-dependent cancer initiation and promotion, but that will not be

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Received 31 March 1997; Revised 30 July 1997; Accepted 7 August 1997

Abbreviations: EMF, electromagnetic fields; RZR, retinoid Z receptor; GnRH, gonadotropin-releasing hormone; EC_{50}, half-maximal activations.

discussed in this review. At normal physiological levels of melatonin, the antioxidant activity would be minimal compared with those of other cellular antioxidants, and therefore loss of melatonin would not be predicted to affect cellular oxidative stress [9]. This paper will focus on melatonin receptor–mediated events that we propose may be involved in steroid hormone homeostasis.

MELATONIN RECEPTORS

Binding studies have demonstrated the presence of specific melatonin receptors in the brain and other cells [10]. The area with the highest concentration of receptors in the brain is the hypothalamus [11]. Autoradiography studies have indicated that specific binding occurs primarily in the suprachiasmatic nucleus (the accepted control site of circadian rhythms), the median eminence, and the anterior pituitary [12–15]; however, other studies have indicated binding throughout the brain [16].

Seasonal rhythms are driven by changes in photoperiod, the most reliable indicator of the season. Melatonin release is also controlled by these seasonal changes and in turn controls circadian rhythms and reproductive cycles in animals that are seasonal breeders [9]. These functions are controlled primarily within the brain by the hypothalamus and non-neurally by the pituitary. However, the mechanism of melatonin action on the brain has only recently been studied. Melatonin administration to animals affects the hypothalamus and causes gonadal regression [17–18]. Melatonin administration also directly affects the pituitary and the production of prolactin [19]. The hypothalamus and the anterior pituitary control steroid hormone production, and therefore possible anti-gonadal effects of melatonin could be elicited through this region of the brain. Furthermore, the presence of high-affinity melatonin receptors within these organs suggests that melatonin's primary actions occur within these organs, and therefore any perturbations in hormone homeostasis and modulation of hormone-dependent cancer rates may be associated with the indirect effects decreased melatonin levels may have upon these processes within the hypothalamus and pituitary.

In the last few years, multiple putative melatonin receptors were cloned [9,20]. These receptors are found in both the membrane and nuclear fractions of cells. To our knowledge, melatonin is the only hormone with both nuclear and membrane receptors, if both receptors are true melatonin receptors. The nuclear receptors are in both the brain and non-neural tissues [20], whereas the membrane receptors are primarily in the brain [9]. The putative nuclear receptors have a lower affinity for melatonin than the membrane-bound receptors do (Table 1). Whether activation of these putative melatonin receptors regulates hormone-dependent cancers, such as breast and prostate cancer, is of considerable interest.

Nuclear Receptors

Nuclear receptors form a superfamily of ligand-dependent transcription factors, which include receptors for thyroid hormone, vitamin D, steroids, and retinoic acid. Most of these proteins are nuclear orphan receptors (meaning their ligands have not been definitively identified), including the two putative melatonin nuclear receptors [20]. These receptors are members of the family of retinoid nuclear receptors and have been designated retinoid Z receptor (RZR) β (which is found primarily in the brain [21]) and RZRα (which is found in non-neural tissues [22]). RZRα is found in B lymphocytes, where binding of melatonin to the RZRα receptor initiates down-regulation of 5-lipoxygenase activity [22]. RZRα is also expressed in liver, smooth muscle, and testes [22]. The breast cancer cell line MCF-7 also expresses RZRα, and melatonin attenuates proliferation of these cells [23].

RZRβ is detected most strongly in the pineal gland, thalamus, and hypothalamus, whereas only the adrenal gland is positive among non-neural tissues, but an extremely low amount of mRNA is detected [21]. The distribution of RZRβ parallels the sites of expected action of melatonin based upon how it affects seasonal breeding and circadian rhythms, because RZRβ is found in regions of the brain that control circadian rhythms and steroid hormone production. This suggests that RZRβ is involved in melatonin action.

Membrane Receptors

There are currently three cloned membrane-bound melatonin receptors [9]. These receptors are coupled to G proteins, specifically the G_i proteins that are responsible for the inhibition of adenylyl cyclase and cytosolic calcium influx induced by gonadotropin-releasing hormone (GnRH) [15,24]. The actions of melatonin on pigment aggregation in *Xenopus laevis*

Table 1. Binding Constants for Melatonin Receptors

Receptor	K_d cloned receptor (pM)	Receptor location	Reference
Mel_{1a}	20–40	Membrane: brain	[9]
Mel_{1b}	160	Membrane: retina	[9]
Mel_{1c}	20–60	Membrane: non-mammalian	[9]
RZRβ	5000	Nuclear: brain	[21]
RZRα	1710	Nuclear: non-neural	[22]

can be antagonized by activation of protein kinase C or protein kinase A [25], further indicating that inhibition of adenylyl cyclase through G_i proteins is responsible for melatonin's inhibitory actions. Of the three distinct melatonin membrane receptor subtypes found in vertebrates, only two, Mel_{1a} and Mel_{1b}, have been cloned in humans [24,26]. One termed Mel_{1c} [9] has been cloned in chickens and frogs but not mammals. The Mel_{1b} receptor is expressed in the retina, whereas the Mel_{1a} receptor is expressed in the suprachiasmatic nucleus and the pars tuberalis of rodent tissues [9,24,26].

Are Both Nuclear and Membrane Receptors True Melatonin Receptors?

The primary weakness with the supposition that the nuclear RZRs are melatonin receptors is their low affinity for melatonin, particularly when compared to the membrane melatonin receptors (Table 1). They have 10–250 times less affinity for the ligand than the membrane receptors, and the approximate concentration of melatonin in the nucleus is less than the affinity constant for the receptors. Melatonin accumulates to concentrations as high as 1 nM in the nucleus [27], while the half-maximal activations (EC_{50}) for RZRα and RZRβ are 1.1 nM and 3 nM, respectively [20,21,28]. The EC_{50} concentration of melatonin for RZRβ is 12 times higher than the nighttime serum concentration and three times higher than the nighttime nuclear concentration [29,30]. It is possible that other chemicals (similar compounds or melatonin metabolites) are ligands for the putative nuclear receptors [21]. Furthermore, the RZR receptors have high constitutive activity in the absence of ligand, which raises the question of whether these receptors actually need melatonin to mediate their response [20].

Although the information indicating that the RZRs have low affinity for melatonin may shed doubt upon whether melatonin is a ligand for the nuclear orphan receptors, it does not rule out the possibility. Melatonin is found at concentrations fivefold to sixfold higher in children 1–3 yr of age than in adults [31] and so may be important in early development. RZR receptors are found in tissues expected to be sites of melatonin action (hypothalamus, gonads, and immune system) and may enhance the activity of the membrane-bound receptors. It has been hypothesized that some of the membrane binding sites may provide an uptake system of melatonin into the cell [11,20]. Carlberg and Wiesenberg [20] hypothesized that the RZRs may be phosphorylated to initiate melatonin's action as a result of activation of the signal transduction cascade by the melatonin membrane receptors or other membrane receptors. However, there are no known cell lines that contain both nuclear and membrane-bound receptors. Furthermore, membrane-bound receptors are found primarily in the brain, and nuclear receptors have been found in both brain and non-neural tissues. Therefore, the hypothesis that the RZRs are phosphorylated in response to melatonin binding to the membrane-bound receptors may be difficult to test in vitro with brain tissue and may be untrue in non-neural tissues due to the absence of membrane-bound receptors.

RELATIONSHIP TO CANCER

Melatonin's possible role in controlling hormone homeostasis and proliferation is of vital interest, especially because the rates of hormone-dependent cancers, such as breast and prostate cancer, are rising. It has been demonstrated for animals and suggested for humans that EMFs and light at night inhibit melatonin production [32–34]. Does this affect cancer risk and how? To properly address these interwoven questions, we must understand the mechanistic theories by which melatonin may act to inhibit carcinogenesis. There are two general mechanisms by which melatonin may affect hormone-dependent proliferation: directly, through interaction with non-neural melatonin nuclear receptors to directly attenuate steroid hormone processes, and indirectly, by affecting steroid hormone concentrations (Figure 1). Below, we propose and clarify a number of molecular mechanisms illustrating how a reduction in melatonin due to EMFs or light at night may modulate growth of hormone-dependent cancers. None of these effects are proven; the purpose of this discussion is to provide a hypothetical framework for the melatonin hypothesis.

Nuclear receptors

EMFs and light at night have been reported to reduce melatonin levels [32] and may repress physiological activities regulated by melatonin. A reduction in melatonin concentration could perturb the immune system by increasing estradiol, increasing 5-lipoxygenase activity, decreasing interleukin-2 release (which would decrease T-helper and natural killer cell activity), and decreasing melatonin's suppressive effects on glucocorticoid production, an immunosuppressor [35,36]. Alterations in innate immune function may reduce tumor surveillance, allowing enhanced tumor proliferation (Figure 2). 5-lipoxygenase enhances growth factor–mediated proliferation in lung cancer cell lines [37] and inhibition of 5-lipoxygenase activity (LTB4 synthesis correlates with decreased mammary tumor production in rats) [38]. Melatonin's repressive control over 5-lipoxygenase activity [22] and other immune system effects may render an important role in inhibiting cancer. For example, activation of RZRα represses 5-lipoxygenase activity [22], and thus depressed melatonin concentrations may increase 5-lipoxygenase activity. Melatonin concentrations are approximately 5.4-fold higher in children than in adults, reaching concentrations averaging 1.4 nM [31]; therefore, the

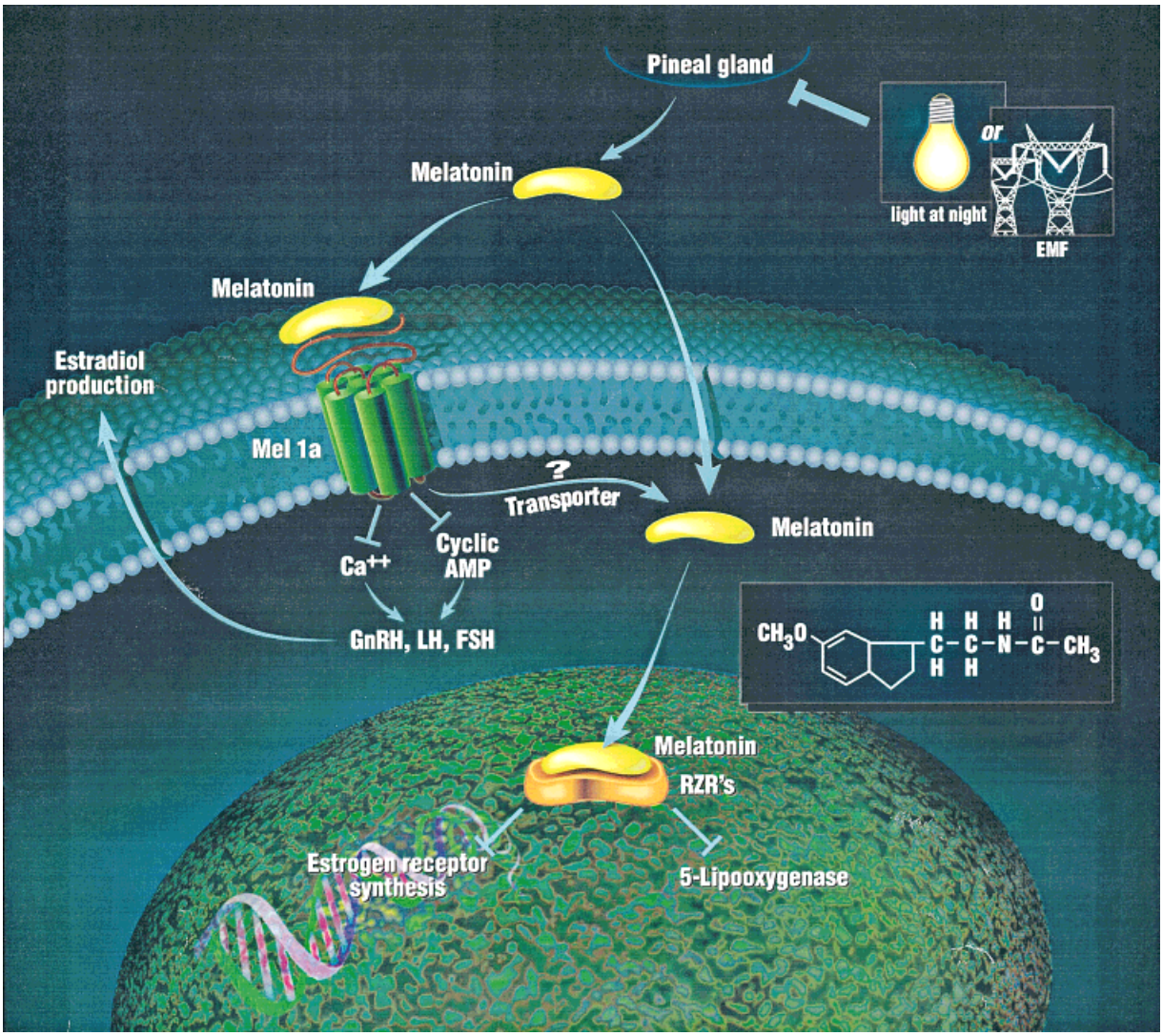

Figure 1. The many hypothesized sites of action of melatonin that may affect hormone homeostasis and ultimately hormone-mediated carcinogenesis. Included are sites within the brain and non-neural sites as well as both nuclear and membrane-bound receptors in cells. LH, luteinizing hormone; FSH, follicle-stimulating hormone.

nuclear receptors may play a more prominent role in children than adults. It is interesting to speculate that reduced melatonin and subsequent increased 5-lipoxygenase activity could play a role in increased childhood leukemia incidence after high exposure to EMFs.

Alternatively, melatonin, through activation of RZRα, may directly inhibit proliferation of estrogen-responsive cells. RZRα is found in MCF-7 cells [20,22], which may account for melatonin's reported ability to downregulate the estrogen receptor and for the proliferation of this cell line [39,40]. Some researchers have been unable to repeat experiments demonstrating inhibition of proliferation in MCF-7 cells by melatonin [41], and recent evidence suggests that the estrogen receptor gene promoter does not contain an RZR response element [20]. Melatonin has also been reported to attenuate proliferation of melanoma cell lines that do not contain detectable estrogen receptors [42]. Thus, melatonin may work through other mechanisms to downregulate proliferation in vitro.

RZRβ is located within the brain, including the hypothalamus. RZRβ displays a pattern of expression similar to that of the membrane-bound receptors, consistent with its effects upon steroid hormone production. Activation of RZRβ by melatonin may downregulate proteins needed for the production and release of GnRH, luteinizing hormone, and follicle-stimulating hormone and ultimately inhibit production of steroid hormones, such as estradiol. Based upon its distributions, downregulation of estradiol

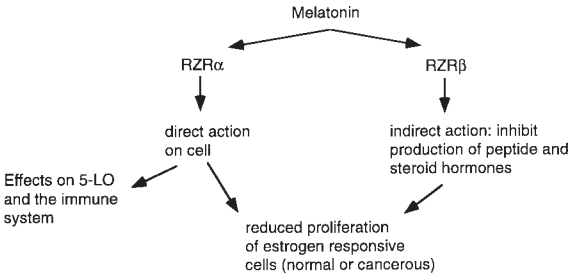

Figure 2. Potential sites of action of the nuclear receptors in hormone-dependent cancer and the immune system. 5-LO, 5-lipoxygenase.

may be RZRβ's expected mode of action; however, speculating on its molecular mode of action is difficult because there are no actions or genes currently known to be controlled by RZRβ. Therefore, it cannot be excluded that RZRβ may work through alternate mechanisms or that it is not a melatonin receptor.

The low affinity of the RZRs for melatonin could mean that melatonin's actions upon these receptors only occur at pharmacological concentrations of melatonin or during childhood. This is paramount to the EMF issue, because it is the loss of melatonin action that is significant, and if action through these receptors does not occur at physiological concentrations of melatonin, then loss of melatonin due to EMFs or light at night would have no consequence. However, it is interesting to speculate that the nuclear receptors play a prominent role during childhood development, which would provide a possible association between childhood leukemia, EMFs, and melatonin.

Membrane Receptors

The membrane-bound melatonin receptors have predicted actions that indirectly influence hormone-dependent carcinogenesis (Figure 3). The membrane receptors (Mel_{1a} and Mel_{1b}) are found primarily in the brain and may inhibit hormone-responsive cancers by inhibiting steroid hormone production. For

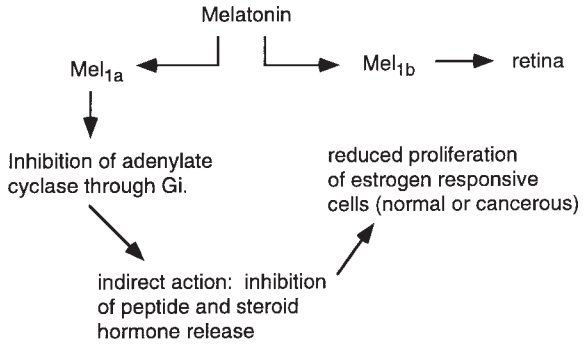

Figure 3. Potential sites of action of the membrane receptors in hormone-dependent cancer and the retina.

example, activation of the membrane-bound receptors inhibits cAMP production and calcium influx and may inhibit release of GnRH from the hypothalamus [18,43], and luteinizing hormone and follicle-stimulating hormone from the pituitary as well as prolactin release [19,44,45]. Subsequent downregulation of the release of these hormones by melatonin would affect 17β-estradiol production and may attenuate proliferation of estrogen-responsive cancers during the promotional phase, as hypothesized by Stevens and Davis [8] and reported by Blask et al. [46].

It is interesting to speculate that melatonin acts in such a manner, because high-affinity receptors are located on both the median eminence of the hypothalamus and the pars tuberalis of the pituitary. Each of these regions controls release of the hormones listed above, providing melatonin two successive sites to inhibit the release of peptide hormones and to regulate production of estradiol and cell proliferation.

If such a relationship exists, then light at night– or EMF-induced loss of pineal function may increase estradiol levels, thereby increasing proliferation of estrogen receptor–positive tissues and cancers. This hypothesis needs more study because it has not been conclusively demonstrated that downregulation of melatonin and its constitutive effects have a significant physiological effect upon these proliferative processes. Perturbations in prolactin release by melatonin may also play an important role in the etiology of breast and other cancers.

RESEARCH NEEDS

Further work needs to be performed to address the questions paramount to the EMF issue, such as does loss of melatonin have a significant effect on estradiol production? If so, is this effect sufficient to influence mammary carcinogenesis, and how much loss of melatonin is needed to elicit this effect? Currently, much of the research has examined pharmacological doses of melatonin. This work has indicated that melatonin can downregulate production of steroid hormones; however, the dose-response relationship between loss of melatonin and increase in steroid hormone production is not known. It will be difficult to discern the complex interactions involving EMFs, melatonin, peptide hormones, and estradiol.

Research needs to be performed to test these theories. While we are examining in more detail melatonin's mechanism of action, we need to address whether and how much loss of melatonin is necessary to promote hormone-dependent carcinogenesis. New technologies can be used to investigate these questions. For example, instead of using pinealectomized animals, knockout mice lacking *N*-acetyltransferase could help elucidate the effect of melatonin loss. Knockout mice lacking the various putative melatonin receptors could also be developed and may be useful in elucidating the effects of mela-

tonin on carcinogenesis. Of course, these tools could also be used to elucidate other actions of melatonin and to examine which receptors are involved in melatonin's reported actions. Use of knockout mice may reveal which receptors are the actual melatonin receptors and which receptors are essential for a normal life and specific physiological and pathological processes.

Other experiments that may be useful include transplantation of hormone-responsive cancer cells into nude mice to elucidate whether melatonin affects proliferation in vivo, whether pulsated light at night induces attenuation of melatonin levels, and what effects light at night has on hormone-responsive cancers.

CONCLUSIONS

This Working Hypothesis proposes a variety of mechanisms by which reduced melatonin concentrations may affect hormone homeostasis and induce breast and other steroid hormone–dependent cancers. Several mechanisms have been considered, such as perturbations in immune system function or loss of direct inhibition of cellular proliferation due to RZRα inactivation. More difficult to discern is whether melatonin affects hormone homeostasis and whether EMFs elicit their ultimate effects by perturbing brain peptide hormones. The only way to conclude whether EMFs have profound consequences on melatonin homeostasis and thus affect hormone homeostasis and cancer is through patience, proper hypothesis testing, and sound science. We hope that this paper provides ideas and the impetus to test whether melatonin has these effects by using some of the new tools available.

ACKNOWLEDGMENTS

We would like to thank Greg Tavlos for his insight while discussing melatonin and EMF. This study was funded in part by a competitive intramural award through the National Institute of Environmental Health Sciences (NIEHS)/Department of Energy (DOE) Magnetic Fields (EMF) Research and Public Information Dissemination (RAPID) Program.

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