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Meditation, Melatonin and Breast/Prostate Cancer: Hypothesis and Preliminary Data*

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Abstract — The objective of this study was to test the hypothesis that the regular practice of mindfulness meditation is associated with increased physiological levels of melatonin. Melatonin may be related to a variety of biologic functions important in maintaining health and preventing disease, including breast and prostate cancer. Previous studies have shown melatonin production is photosensitive and we suggest here that it also may be psychosensitive.

A cross-sectional study of 12-hour (20:00 – 08:00) urinary 6-sulphatoxymelatonin was conducted from which we analyzed data from 8 women who regularly meditate (RM) and 8 women who do not meditate (NM). All samples were collected in the homes of study participants. Volunteers were recruited to provide 12-hour overnight samples of urine. All subjects collected the samples on one night during the same 1-week period. There was no explicit intervention. However, all RM were either graduates of, or teachers in, the University of Massachusetts Stress Reduction and Relaxation Program.

The main outcome measure was the total excretion of urinary 6-sulphatoxymelatonin. Multiple linear regression (Proc GLM in SAS) was performed to test the effect of meditation (RM vs NM) on 6-sulphatoxymelatonin.

The results of the study were that after controlling for the non-significant effect of menstrual period interval, we found an effect of meditation group (RM vs NM: $b = 1.983$; $F = 6.78$; $p = 0.02$) and age (for each integer year: $b = -0.169$; $F = 8.41$; $p = 0.01$). The conclusion is that study results are consistent with our hypothesis and indicate that melatonin might be a useful parameter in testing similar psycho-social interventions. Given that two intervention studies have provided support for the concept of psycho-physiological interactions in survival among cancer patients, applications of our findings might be pertinent to the area of breast and prostate cancer.

Hypothesis and summary

We propose that regular practice of meditation as taught in the Stress Reduction and Relaxation Program (SR&RP) of the University of Massachusetts Medical Center (UMMC) is associated with increased physiological levels of melatonin. Melatonin, an indoleamine produced in the pineal gland, may be re-

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lated to a variety of biologic functions important in maintaining health and preventing disease. Previous studies have shown that melatonin production is photosensitive and we suggest here that it may also be psychosensitive. We present preliminary data to support this hypothesis and suggest testing applications of this finding in the area of breast and prostate cancer.

Introduction

Mind-body medicine recently has received attention both in the popular media and in scientific and public policy arenas, resulting in the establishment of the Office of Alternative Medicine at the US National Institutes of Health. Further support for the concept of psycho-physiological interactions in healing has been provided by two studies showing improved survival associated with psycho-social interventions for cancer patients, one involving metastatic breast cancer (1) and the other involving malignant melanoma (2). In the former study, which was an ad hoc analysis, physiological parameters were not measured; in the latter study none of the immunological parameters showed a persistent significant change following the intervention, although melatonin was not measured. The mechanism for how such interventions might act at a physiological level has yet to be elucidated. We propose that the mechanism may involve altered or enhanced melatonin levels.

In 1641, Descartes postulated that the pineal gland was the seat of the soul and presented it as the activating principle, or confluence, of psyche and soma (3). Despite the implicit potential for psycho-physiological interactions, to our knowledge no study of any psycho-social intervention has used melatonin as a study endpoint. One of us (J.T.) developed this hypothesis. To gather preliminary data in support of a formal test of the hypothesis, we chose to compare overnight production of melatonin in meditating and non-meditating women.

Background

Meditation

For the purposes of this review, we are using the operational definition of meditation as the intentional self-regulation of attention in the service of self-inquiry. The review includes studies using various forms of meditation, with some emphasis on mindfulness meditation since we are most familiar with that practice and because our intervention is based on it. Mindfulness is one of the core practices of Buddhist meditation and can be defined as paying attention non-judgementally on purpose in the present, from moment to moment. Since the capacity to attend in this way is a universal, if not highly developed, attribute of all human beings, mindfulness has a potential relevance far beyond its Buddhist context.

The SR&RP is a well-established meditation-based program which has been in operation at UMMC for the past 15 years and has provided to more than 6000 physician-referred patients with a wide array of medical/psychiatric problems, including chronic pain, cancer, hypertension, psoriasis, gastrointestinal problems and anxiety. The program is based on intensive training in mindfulness meditation. The SR&RP is structured in the form of a course given in class sessions to groups of 25–30 people. The framework is educational rather than psychotherapeutic and includes regular practice at home of approximately 45 min daily (4).

Past studies have shown that the SR&RP is effective for people with chronic pain (5–7) and anxiety disorders (8). In addition, a preliminary study indicates that it is effective in the treatment of psoriasis (9).

Meditation and cancer. Although there have been no controlled randomized trials of meditation used with cancer patients, two studies have been done with psycho-social interventions that included components similar to meditation. One involving a group of subjects with malignant melanoma used a short-term intervention consisting of education, enhancement of problem-solving skills, psychological support and stress management (including several relaxation techniques) (2). At a 6-year follow-up, there was a significantly lower death rate among intervention compared to control subjects (2). The other study showed that 1 year of a weekly group therapy intervention was associated with improved 10-year survival rates for women with metastatic cancer (1). The intervention, Supportive/Expressive Group Therapy (10), included a self-hypnosis exercise and stress management technique called 'simple breath awareness exercise for those who are not highly hypnotizable' (10), which is essentially a very low dose of mindfulness meditation practice as taught in the SR&RP.

Melatonin

The synthesis of melatonin occurs primarily in the pineal gland (11). Pineal activity is photsensitive, with levels of melatonin rising to a plateau between approximately midnight and 3 a.m. (11, 12). The pineal gland acts as a transducer of light, converting light

into electrochemical signals that modulate reproductive, adrenal and other neuroendocrine interactions as well as immune function (13). The pineal gland and melatonin are involved in the regulation and timing of reproductive, developmental, and ageing processes (14). It has been noted that melatonin is produced in highly diverse organisms from unicellular algae to humans, suggesting that it has been evolutionarily conserved and may be important in basic cellular physiology (15).

Evidence has accumulated to support the role of melatonin as an anti-physical stress hormone (16–20). In a variety of animal models, the effect of physical stressors (gastric ulcers and restraint) was decreased by the administration of melatonin (16, 18, 19, 21). A study of social stress in animals showed associated changes in melatonin levels (22).

Melatonin may act as an immunomodulatory agent, with its effects mediated through the release of opioid peptides and interleukin-2 (IL-2) by T-helper cells (13, 21). The accumulated evidence suggests a bidirectional interaction in which pineal melatonin influences immune functions and some immune signals, such as interferon-gamma, have an enhancing effect on pineal function (13). This is supported by the report of specific binding sites for melatonin on human B and T lymphocytes, with melatonin acting directly to potentiate the effect of vasoactive intestinal peptide in activating cyclic AMP production in the lymphocytes (23–25), and high affinity melatonin receptors on human malignant melanoma cells (26, 27).

Melatonin and cancer. Melatonin has been shown to be the most powerful and effective endogenous hydroxyl radical scavenger detected to date (14, 28–30). One study provided direct evidence for the dose-dependent role of melatonin in protecting against DNA damage from the hydroxyl radical-generating carcinogen safrole (28). This is of great importance because the hydroxyl radical is the major mediator of oxidative damage and has been implicated in the free radical theory of ageing and carcinogenesis (14).

Melatonin and other pineal substances have been shown to be potent oncostatic agents which inhibit growth of a wide range of neoplasms in animal and human in vivo and in vitro models, with the most abundant and promising evidence being in the area of breast cancer (27, 31, 32). In vitro studies of breast cancer have shown that melatonin has a primary direct effect of inhibiting proliferation of estrogen-responsive MCF-7 human breast cancer cells (27, 32). Melatonin's antiproliferative effect appears to be mediated through the estrogen receptor and the estrogen response pathway of the breast tumor cell (32). Also, MCF-7 cells incubated with melatonin showed increased estrogen receptor binding activity (33). In MCF-7 cells, melatonin's effect was cell cycle specific, causing a G_1-to-S phase transition delay (27, 34).

Melatonin has been shown to share several characteristics with tamoxifen, a non-steroidal antiestrogen which is a clinically important treatment for estrogen-receptor positive breast cancer (34, 35). Melatonin has been hypothesized to be the body's endogenous antiestrogen, whereas tamoxifen is an exogenous antiestrogen (27, 34). Both tamoxifen and melatonin inhibit breast cancer cell growth in vivo and in vitro by interfering with the estrogen-response pathway and their inhibitory effects appear to be specific for the same cell cycle phase (27, 34, 35). Two of three studies by Blask and colleagues, using different in vitro experimental conditions, showed a synergistic effect of melatonin and tamoxifen (32, 34, 35). Notably, pre-treatment with melatonin (prior to adding tamoxifen) resulted in a 100-fold increase in the inhibition of breast cancer cell growth (35). Blask suggested that melatonin might be used in combination with tamoxifen in treating breast cancer (36). There is an ongoing trial in the Netherlands using melatonin-progesterone as a contraceptive and possible breast cancer preventive (36, 37).

In the aggregate, clinical studies looking at circadian rhythms of melatonin in women with breast cancer suggest that the night-time rise in melatonin is suppressed in women with breast cancer (27). There is some indication that the ability to maintain normal or elevated levels of melatonin is associated with a successful outcome in coping with breast cancer (27). A two-fold higher melatonin level was associated with breast tumors having a low proliferative index compared to those with a high index, suggesting that hypersecretion of melatonin would predict a more favourable prognosis (27, 38).

Results of a preliminary non-randomized study of a group of patients with metastatic solid neoplasms of various types that were unresponsive to chemotherapy indicated that orally administered melatonin might exert its immunostimulatory effects only when given with IL-2 and the majority of these effects were greater than those in patients treated with IL-2 alone (39). The investigators concluded that the mechanism of melatonin action is to enhance IL-2-mediated immune effects rather than inducing them (39).

Increasing melatonin levels were predictive of a favourable response to chemotherapy in a group of cancer patients, some of whom had breast cancer (40). The same investigators conducted several preliminary and two randomized studies of groups of patients with a variety of cancers, most of them unresponsive to

standard chemotherapy or other anticancer therapies, who were given either melatonin or melatonin with IL-2 (41–44). In one of the randomized studies, using patients with brain metastases due to solid neoplasms, those treated with melatonin compared to supportive care alone had a significantly greater survival at 1 year, longer free-from-brain-progression period, and longer mean survival time, along with significant improvement in their Karnofsky Performance Status score (44). In the second randomized study, melatonin combined with IL-2 was associated with a significant improvement in immune parameters and a higher rate of survival at 1 year, compared to IL-2 given alone (43).

Prostate and breast cancer are similar in that both are sex hormone-dependent (45–47). Though the evidence is less abundant than with breast cancer, there have been several in vivo studies using a transplantable rat prostate tumor and showing that melatonin injections inhibited androgen-sensitive tumor growth (27, 48). One study showed that 2 out of 3 tumor types were inhibited by late afternoon injections of melatonin (27). A later study which used larger afternoon doses of melatonin showed that tumor weight in melatonin-treated intact animals was less than 50% of that in vehicle-treated animals and the tumor doubling time was increased by 2 days (48). In addition, there was a 50% reduction in circulating testosterone, although testis size remained normal. The investigators hypothesized the mechanism to be a decrease in circulating testosterone or inhibition of tumor proliferation. In androgen-insensitive rats, the results were more mixed (27, 49).

In human studies, the nocturnal melatonin peak was found to be absent or depressed in men with primary prostate cancer compared both to normal controls and those with benign prostatic hypertrophy (46, 47, 50). The investigators suggested that exogenous melatonin might be an appropriate therapy for prostate cancer (51). To our knowledge, no one has conducted such a trial for men with prostate cancer as yet. High doses of exogenous melatonin (100 mg/d) have been shown to potentiate the testosterone-induced suppression of luteinizing hormone in normal men (52). Notably, several of the hormonal anti-testosterone agents used in prostate cancer therapy appear to act by a similar mechanism (53).

In 1976, Relkin hypothesized that the pineal gland becomes hyperactive as an early response to neoplastic disease, by secreting substances such as melatonin (54). Melatonin levels later decrease with disease progression (54). For both breast and prostate cancer, low melatonin levels have been interpreted as indicating an exhaustion of the pineal's ability to respond at progressive cancer stages (27, 46, 47, 50).

Melatonin and meditation

Although melatonin has not been used as an outcome measure in any psycho-social intervention study, indirect evidence from one study showed that regular practitioners of Transcendental Meditation had higher daytime levels of the serotonin metabolite 5-hydroxyindole-3-acetic acid (5-HIAA) compared to controls, and the levels increased following meditation (55). However, the report was based on 5-HIAA concentration in urine rather than total excretion. Serotonin is a precursor of melatonin and has psychoactive properties of its own. In a separate review that commented on this study, the author hypothesized that the reported rise in serotonin was due to enhanced pineal activity (56). In addition, a hypothesis linking endogenous pineal compounds with physiological changes associated with dreams briefly mentioned that melatonin might be generated in meditative states (57).

Meditation and melatonin share several physiological effects, including: analgesia (5–7, 21, 58, 59), anti-stress (e.g. pain as stressor with regard to meditation, and physical stressors such as gastric ulcers and restraint with regard to melatonin) (5–7, 16, 18, 19, 21), anti-insomnia/hypnotic (60–63), anxiolytic (probable for melatonin) (8, 63, 64), and decreased heart rate and blood pressure (65–67). Mediation of some effects via the endogneous opioid system has been shown for melatonin. There is indirect evidence for meditation, in that the SR&RP is particularly effective for patients with chronic pain (5–7) and amelioration of pain is known to involve the opioid system. Also, small but significant and reproducible increases on Kobasa's Stress Hardiness Scale were found among 582 consecutive patients with a wide range of medical conditions who completed the 8-week SR&RP intervention, a change which was maintained at 3-year follow up; patients who were referred to the SR&RP but did not complete the program showed no change between initial referral and 3-year follow-up (68).

Both meditation (60) and melatonin (61–63) have been effective in treating insomnia and inducing or improving sleep. Also, the SR&RP has been found to be very effective for patients with panic disorder and generalized anxiety disorder (GAD) (8), which may be related to a change in gamma-aminobutyric acid (GABA). The pineal gland has $GABA_A$ receptors and actively synthesizes and metabolizes GABA

(64). Melatonin has been shown to significantly increase the inhibitory effect of GABA and to have a benzodiazepine-like activity (63). This suggests a potential anxiolytic and anti-insomnia function for melatonin, the pineal gland, or both. The etiology of GAD is linked to the $GABA_A$ receptor and one of the main pharmacologic treatments for both GAD and insomnia are the benzodiazepines, which interact at this receptor (69).

Preliminary data

A study enrolled 18 healthy women to examine the effect of meditation on melatonin levels measured in overnight (i.e. 12-hour) urines. We chose to focus exclusively on women because we wished to eliminate any extraneous effects of gender and because we are especially interested in breast cancer. Urinary 6-sulphatoxymelatonin excretion is a good index of plasma melatonin levels and it is useful in measuring the amount of melatonin produced and metabolized during the night-time peak and plateau of melatonin levels (70, 71). Urine collection is non-invasive and minimally stressful. Urine samples were analyzed for 6-sulphatoxymelatonin using a radioimmunoassay at Oregon Health Sciences University, USA.

All recruitment and sampling procedures were approved by UMMC's Institutional Review Board. After explaining the purpose of the study, we solicited volunteers to provide 12-hour (20:00 – 08:00) urine samples. Of the 18 women enrolled into the study, all were disease-free and all but one were premenopausal. Ages ranged from 31–54 years. The 10 meditating women were RM (meditating 5–7 sessions/week, 30–45 min/session). The other 8 were NM. All of the meditators had received training in the SR&RP and/or were instructors with that program, and all practiced mindfulness meditation, as described earlier.

We compared 8 of the 10 RM women (2 urine samples were lost) with 8 NM women. In order to account for interval since last menstrual period and age effects, we fitted a regression model using PROC GLM in SAS (72). Meditation group (RM vs NM) was fitted as a dummy variable, and interval since last menstrual period and age were fitted as continuous predictors. Based on type III sums of squares (i.e. the orthogonal model where each effect is treated as thought it were entered last), our results showed that there was no significant effect of menstrual period interval. However, there was a significant effect of meditation group (i.e. in comparing RM to NM: $b = 1.983$; $F = 6.78$; $p = 0.02$) and age (for each integer year: $b = -0.169$; $F = 8.41$; $p = 0.01$). Comparison of total excretion of overnight urinary 6-sulphatoxymelatonin levels in the two groups (using LMEANS in PROC GLM, where we controlled for age and menstrual period interval) revealed a significant difference between mean 6-sulphatoxymelatonin levels in the RM women (7.615 μg/12 h) and the NM women (5.632 μg/12 h) ($t = 2.60$, $p = 0.02$). Data are presented in the Table.

Table Comparison of urinary melatonin metabolite 6-sulphatoxymelatonin values in meditating and non-meditating women

	Subject		*Age (yr)*	*Days from last menstrual period*	*Amount 6-sulphatoxymelatonin in urine (μg)**
Meditators					
	RM	1	53	24	6.188
		2	50	19	4.347
		3	45	19	6.375
		4	45	13	7.896
		5	40	6	9.360
		6	43	19	9.130
		7	31	17	8.580
		8	39	7	7.440
Non-mediators					
	MN	1	42	9	4.140
		2	37	6	7.844
		3	31	26	8.190
		4	46	14	4.810
		5	39	23	3.705
		6	36	22	7.854
		7	47	8	4.140
		8	54	-	5.978

*Concentration x amount.

Conclusion

Although these data are from a small pilot study, the findings argue for continuing research on this important topic. The results we obtained are consistent with the hypothesis that the pineal gland is psychosensitive and that the practice of meditation is associated with increased levels of melatonin. To the best of our knowledge, these are the first data suggesting such an effect. Even with the limitation of self-selection, we feel these are encouraging data on which to build future research efforts. Randomized trials will be required to establish our hypothesis.

Our hypothesis and preliminary data suggest that melatonin may be a relevant outcome variable in assessing psycho-social interventions, particularly for subjects with breast or prostate cancer. Furthermore, exogenous melatonin may be a useful therapeutic agent for advanced cancers of these and other types. We invite other investigators to include melatonin as an outcome variable in similar studies of psychosocial interventions or other interventions for the treatment of breast and prostate cancer.

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