A generalized theory of carcinogenesis due to chronodisruption

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Submitted: 2008-09-29 Accepted: 2008-10-19 Published online: 2008-12-29

Key words: **chronodisruption; light; melatonin; cancer; theory; blindness; shift-work; transmeridian flight; Arctic; sleep**

Neuroendocrinol Lett 2008; **29**(6): 815–821 **PMID:** 19112396 NEL290608R01

REVIEW

Abstract

For two decades, research has been suggested and conducted into the causation and development of cancers in seemingly diverse and unrelated populations such as blind individuals, shift-workers, flight personnel, Arctic residents and subsets of sleepers. One common denominator of these investigations is "melatonin". Another common denominator is that all these studies implicitly pursued the validity of the so-called "melatonin hypothesis", of a corollary and of associated predictions which can be united in our proposed theory of "carcinogenesis due to chronodisruption". The new theory suggests that the various predictions investigated between 1987 and 2008 represent different aspects of the same problem. Indeed, abundant experimental evidence supports the notion that the final common cause of many cases of cancer may be what has been termed chronodisruption (CD), a relevant disturbance of the temporal organization or order of physiology, endocrinology, metabolism and behaviour. While melatonin as a key time messenger and time keeper can be a marker of CD, it is probably only partially related to the differential cancer occurrence apparent in individuals who chronically or frequently experience an excess or deficit of chronodisruption.

> "…. circadian rhythms are inherent in
> and pervade the living system
> to an extent that
> they are fundamental features of its organization;
> and to an extent that if deranged they impair it".
> *- Colin S. Pittendrigh [1960]*

Introduction – why a theory?

In science, a theory is a logical framework which describes the cause-effect-relationships of natural and man-made phenomena. A theory bases itself on observations or replicated facts – be they from observing the natural world or from controlled laboratory experiments. It incorporates available observations and facts and can bring together several hypotheses and corollaries in a logical way, allowing the generation of new testable predictions. In doing so, a theory extends more-narrow hypotheses and allows the more precise predictabil-

ity of facts or observations beyond what was thought to be causally related before.

Intriguingly, in the past two decades, various predictions of cancer causation evolved from the so-called "melatonin hypothesis" [hereinafter referred to as melatonin hypothesis; Cohen *et al*. 1978; Stevens 1987] and an associated corollary. When being investigated under very different circumstances, each prediction following from "light-at-night suppresses melatonin and increases cancer risks" or "deficits of light enhance melatonin production and decrease cancer risks" has found support by some objective evidence. Now, since scientific thinking and rationale that survives experimental testing and observations can become a scientific theory, we think that it is time to consolidate hypothesis, corollary and predictions which represent different aspects of the same central truth in one generalized framework. Note that the following theory unifies seemingly diverse predictions in a logical mechanistic way which can lead to new and promising approaches to cancer research and prevention. Note also that "the melatonin rhythm", being "both a clock and calendar" [Reiter 1993], provides a cornerstone of this theory.

The generalized Chronodisruption-Cancer-Theory

We propose the theory that chronodisruption [CD], defined as the disruption of the temporal organization or order of biological rhythmicity over days and seasons [Erren *et al*. 2003], can predispose to and be a cause of cancer. As the basis for this theory, we will synthesize **I Experimental Evidence** and summarize **II Epidemiological Predictions**. By answering **III How can the CD-Cancer-Theory explain Today's Experimental and Epidemiological Findings?** and **IV Which Novel Predictions, Tests and Directions for Research follow from the Chronodisruption-Cancer-Theory?** we will examine the theory's explanatory and predictive power.

I Experimental Evidence

With regard to melatonin, abundant insights from basic, applied, and clinical research suggest, almost unambiguously, that the pineal indolamine can have anticancer properties via a uncommonly wide variety of mechanisms [Reiter 2004; Erren 2005]. With regard to carcinogenesis, this paper focuses on the breakdown of temporal organization, i.e., the physiologic phasing of biological rhythms over 24 hours and over the year. This, our emphasis, will highlight melatonin's role as a key endogenous messenger of biological time and can explain its critical role for the timing and sequencing of biological rhythms [Erren *et al*. 2003].

For decades, it was known that light is a key *Zeitgeber* and that visible electromagnetic radiation is the key suppressor of melatonin production and secretion in the pineal gland. Importantly, under natural photoperiodic conditions, the circadian rhythms of melatonin can provide clock (24 hour) and calendar (seasonal and yearly) information for many species, including humans [Reiter 1993].

In the following paragraphs, we will describe melatonin's quality of being a critical endogenous time messenger and thus explain melatonin's central role in CD, a relevant disturbance of the circadian organization of physiology, endocrinology, metabolism and behaviour, which links light, biological rhythms and the development of cancers in experimental animals [Straif *et al*. 2007; Erren *et al*. 2003, 2008].

Under regularly recurring periods of light and darkness, as experienced by animals in their natural habitat, melatonin, as a manifestation of the activity of the biological clock, exhibits highly regulated day:night fluctuations in melatonin synthesis and secretion by the pineal gland. This being the case, the daily melatonin rhythm provides precise time of day, i.e., clock, information for the adjustment of appropriate physiological responses [Reiter 1993]. Additionally, for species living under natural conditions, seasonal changes in the duration of day and night length, the magnitude of which are dependent on the latitude at which the organism resides, also provides precise time of year, i.e., calendar, information which likewise determines annual changes in physiology, e.g., fat deposition, reproductive alterations, et cetera.

Humans, due to their capability to alter environmental factors which regulate the biological clock and the circadian melatonin rhythm have subverted the function of the major environmental variable that provides order and stability to the circadian system. Thus, due to the widespread use of artificial light sources and frequent transmeridian travel across multiple time zones, the human species has changed the photoperiodic environment to the extent that the biological clock can no longer provide accurate information about either the time of day or time of year, i.e., it exhibits CD.

Obviously, CD can occur at both the daily and seasonal level with the consequences of these perturbations potentially being increased pathophysiology. To date, altered daily disruptions of rhythmicity have been linked to an increased cancer risk in both women and men [colorectal and endometrial cancer in Schernhammer *et al*. 2003 and Vismanathan *et al*. 2007, respectively; meta-analyses of breast and prostate cancer in Erren *et al*. 2008]. Similarly, distortions of the circannual photoperiod may likewise have health consequences as evidenced by the elevated incidence of depression in people living at the extremes of latitude [Hanson *et al*, 2008]. That misinformation provided by a light-polluted environment might lead to pathophysiological responses,

including cancer, should not be surprising in view of the ubiquitous distribution of cellular melatonin receptors [Dubocovich and Markowska 2005] as well as the ability of the indolamine to function independently of receptors in all cells [Tan *et al*, 2007].

II Epidemiological Predictions

Against the background of abundant experimental insights, epidemiologists have investigated the validity of a number of predictions derived from the original melatonin hypothesis ["light-at-night suppresses melatonin and increases cancer risks"] and an associated corollary ["deficits of light enhance melatonin and decrease cancer risks"].

(i) The blindness prediction

Already in 1992, it was proposed that blind people, perceiving less or no light visually when compared with the sighted [Coleman *et al*. 1992], should have higher melatonin concentrations. The prediction that blind people have therefore lower breast cancer risks was investigated subsequently in six observational studies. Taken together [(a review of 5 studies up to 2001 in Erren 2002; Pukkala *et al*. 2006], the evidence is certainly compatible with the validity of the prediction. And yet, in view of the rather special life conditions of blind people, findings may not be securely generalizable to wider populations.

(ii) The shift-work prediction

During shift-work and, in particular, during night shifts, the use of artificial light sources and activities provide our central circadian pacemaker with inappropriate and confusing information. Two related consequences, namely desynchronization of biological rhythms and the overall suppression of darkness-related melatonin production and release [Reiter *et al*. 1992; Jasser *et al*. 2006] have been hypothesized to increase breast cancer risks in women and prostate cancer risks in men [Erren *et al*. 2003; Stevens *et al*. 1992; Erren 2002]. While meta-analyses of 7 studies in women and two investigations in men are compatible with increased breast (40%) and prostate cancer risks, there is no doubt that future epidemiological studies must appreciate details of shift-work and of covariates for the development of the diseases [Erren *et al*. 2008]. This also applies to the necessary follow-up to two studies evincing increased risks of colorectal [Schernhammer *et al*. 2003] and of endometrial cancers [Vismanathan *et al*. 2007] in some night shift-workers.

(iii) The transmeridian flight prediction

In addition to shift-work exposures, rapidly changing external light or time cues during extended transmeridian travel can lead to pronounced internal desynchronization of orderly biological rhythms. Filipski and colleagues (2005) explicitly commented that their experimental evidence showing that molecular clocks in tumors could be significantly altered via the disruption of regular photoperiodic synchronization may have clinical relevance with regard to cancer risk in individuals exposed to iterative transmeridian flights. Epidemiologically, Mawson [1998] and Pukkala *et al*. [2003] proposed that chronic interruptions in circadian rhythms or CD may be a possible explanation for moderately elevated breast and prostate cancer risks in some studies of female and male flight personnel, respectively. Compatible with this notion, meta-analyses of 21 epidemiological investigations of flight personnel suggested a 70 and 40% increase in the risk of breast and prostate cancer, respectively [Erren *et al*. 2008].

(iv) The latitude prediction

In 1999 [Erren *et al*. 1999], it was suggested that winter darkness in the Arctic should increase residents' melatonin levels and this is indeed the case [Stokkan *et al*. 1994; an overview in Erren 2002]. The prediction that hormone-dependent cancers should therefore occur less frequently in people living north rather than south of the Arctic Circle was supported by epidemiological data. However, these ecologic observations were severely limited in scope and in methodological weight. Importantly, therefore, the prediction was extended in 2001 [Erren *et al*. 2001] insofar as it was suggested that melatonin levels and rhythms vary between people who are differentially exposed to light by virtue of variations in ambient photoperiods. Hitherto, this approach of a "light dosimetry by geography" has not been pursued. And yet, the proposed research for a biomarker study of healthy general populations in a wide range of latitudes would be ".... essential research that will characterize light exposures, melatonin cycles, and circadian rhythms from the Arctic to the Mediterranean, in a systematic and comprehensive way, to supplement what now exists primarily as a scattered set of small studies and isolated reports. It will not answer any questions about cancer and light, but solid research to answer those questions will not be able to be designed sensibly without the information this crucial baseline study will produce" [Poole 2002].

(v) The sleep length prediction

On the assumption that sleep duration could be expected to correlate positively with individuals' cumulative melatonin levels, it was predicted that cumulative time at sleep may correlate significantly with disease [Erren 2002; Stevens 2002]. While it is of interest that epidemiological research published thereafter found some support [Verkasalo *et al*. 2005] for lower breast cancer risks in long sleepers in a Finnish study, there was no convincing evidence for an association between sleep duration and the incidence of breast cancer in a large American investigation [Pinheiro *et al*. 2006]. And, with regard to mortality rather than breast cancer risks, a recent individual study [Patel *et al*. 2004] and a 2004

review [Youngstedt *et al*. 2004] suggested that observational evidence is complicated insofar as the mortality risk in women was lowest among those sleeping 6 to 7 hours and that sleeping beyond 8 hours could even be associated with increased mortality, respectively.

III How can the CD-Cancer-Theory explain Today's Experimental and Epidemiological Findings?

We have put forward primarily positive evidence for the predictions (i) to (v) and pointed to possible limitations of the observational studies and their interpretation to-date. We think that there is one logical explanation for the given set of experimental facts and epidemiological observations and propose that the differential cancer risks observed are due to chronodisruption.

On the basis of our proposed theory we explain the experimental findings and epidemiological observations as being a breakdown of phasing internal biological systems appropriately relative to the external, i.e., environmental changes. This is actually in line with some thoughts provided by Colin Pittendrigh almost 5 decades ago [Pittendrigh 1960]:

> "This breakdown [of circadian organization] is in all probability a failure of mutual entrainment among constituent oscillatory subsystems leading to their dissociation and a loss of normal phase relationships. I should be explicit that the statement that damage commonly develops in aperiodic regime is fact".

At the time, Pittendrigh offered – as "one fully direct demonstration" of his proposition "that loss of proper phasing among physiological subsystems is detrimental" a reference to the possible first documentation of CD-associated cancer in an experiment. In a section headed "The physiology of circadian organization; and its breakdown" Pittendrigh wrote:

> "Previous well-known studies of [Harker 1956] had already demonstrated an autonomous daily rhythm in the release of neurosecretion from the cockroach subesophageal ganglion which persists even when this organ is explanted into the body cavity of other roaches. Harker has now shown that when such supplementary ganglia are daily implanted into the abdomen of an intact host roach they cause no damage if implant and host are *in phase* as to their circadian oscillations. If, however, the implant is 12 hours out of phase with the host, the latter develops transplantable tumors in the mid-gut wall which lies below the out-of-phase implant".

Clearly, many (or all) of the suggested anti-cancer properties of melatonin could play a key role in the summarized experiments and epidemiological observations but, equally clearly, this paper's theory focuses on one particular, of the many, facets of the pineal indolamine. The CD theory postulates that it is the circadian organization or order of biological rhythms which goes wrong and can ultimately lead to cancer – since melatonin appears to play a key role as a time messenger within organisms, the logical framework should not be confined to the original melatonin hypothesis. Rather, by encompassing melatonin as a key time messenger and recognizing the pivotal role of the pineal gland and its connections with circadian master clocks in our brain, viz the suprachiasmatic nuclei [SCN], the theory is extended to chronobiological considerations of physiologic order or pathological disorder and not confined to suggestive other actions of melatonin.

Indeed, to conclude that a reduced amount of melatonin or an alteration in its circadian rhythm is solely responsible for the reported elevated earlier cancer incidence in night shift workers and in frequent transmeridian travelers would seem overly simplistic. It is more likely that distorted complex interactions of a variety of factors, one of which is the altered melatonin cycle, contribute to the mediation of damaging molecular events that provide the basis for the subsequent initiation and growth of a tumor. Unraveling the myriad of disturbed cyclic events that are involved in the oncogenic process in individuals suffering with CD, although difficult, would well be worth the effort if it leads to a means of forestalling or preventing the cancers that have been associated with persistent CD.

IV Which Novel Predictions, Tests and Directions for Research follow from the Chronodisruption-Cancer-Theory?

A theory should permit predictions that are different from those derived from its predecessor. Now, with regard to the CD-Cancer-Theory, we would suggest that investigations focus on relevant signs of CD; we should refine our – experimental and epidemiological – studies with a view to overt indications of CD beyond melatonin alterations or surrogates of possible or likely CD exposures such as shift-work status alone. In other words, the CD theory requires the rejection of a long-lasting focus on melatonin's "traditional anti-cancer properties" alone and leads to a substantial extension – both of complexity and of predictive power. This is actually in line with what one of the scientists of the IARC meeting in Lyon in October of 2007 wrote with regard to shift-work and circadian disruption, namely "The pineal hormone melatonin appears to occupy an important, but not exclusive, role in oncoprotection" [Haus 2007].

It is already documented that several psychological [Lee *et al*, 2007; Volpe *et al*, 2008] and metabolic [Raschka *et*

al, 1998; Nomura *et al*, 2001; Sonnerberg, 2008] diseases have a seasonal onset component. Perhaps these are, in part, a result of disrupted normal cycles imposed by the extreme photoperiodic conditions of high latitudes. If this is the case, it would not be unexpected that cancer may also be linked to the marked exaggeration of photoperiodic changes experienced at the extremes of latitude. While this may be difficult to determine since tumours often do not become manifested until years after the initiating event, it should not be disregarded as a possibility.

Now, what follows with regard to further observational research from the CD-Theory? More generally, we should be under no illusion: if the theory of CD is "right", "testing" any one of the epidemiological predictions to-date will not only be complicated by the necessity to consider other explanations for risk findings than melatonin exposures and CD but, importantly, by the fact that combinations of (i) – (v) could be, and most likely are, relevant. For instance, light dosimetry by geography may not only be relevant to elucidate effects of differential light exposures on melatonin and disease development in their own right (it is conceivable that natural light exposures may co-determine the geographical distribution of health and disease in man) but also because latitude (as a proxy for ambient light exposures) may have to be controlled for when comparing and, indeed, interpreting, study results from geographically different areas. A further example may be "sleep length" and quality or depth of sleep which could be a critical exposure variable *per se* but also very important for comparing risk studies in various populations. Indeed, the individuals' sleeping time might have to be considered in studies which contrast groups with assumed major differences in their average exposures to light, e.g., night shift-workers versus other workers or the blind and visually impaired versus others [Erren 2002].

Persuasive suggestions which will be applicable in epidemiological practice as to what to study, how and in whom are more than welcome. Given the considerable remaining gaps of knowledge on the one hand and the possible public health impact of melatonin- and rhythm-related diseases on the other, they seem to be a must. One possible step in the appropriate direction could be to have IARC and/or the NIEHS convene an authoritative panel of epidemiological and experimental researchers to develop comprehensive exposure metrics for chronodisruption research [Erren *et al*. 2008]. Such an initiative could be crucial to avoid possibly dozens of studies in the near future employing incomparable and conceivably uninterpretable exposure assessments.

But, more specifically, the critical question to us is the following: "How can we more appropriately investigate CD and its effects in experimental and in epidemiological studies?" What signs or variables could identify relevant CD? Experimental studies will be important to identify variables which may then be used in epidemiological research. Preferably, we would use biomarkers of effect but presumably we will have to work with biomarkers of exposure. In any case, rather than focussing on melatonin and its "classical anti-cancer properties", further parameters which indicate or reflect temporal organization patterns should be identified and tested. Mechanistic candidates should then be incorporated in epidemiological research, in particular of cancer developments over decades. For the time being, epidemiological studies which investigate cancer developments over decades might have to continue to focus on relevant surrogates of CD exposures – be they work at unusual times and/or unusual sleep patterns.

In principle, a theory is conceptualized as providing a logical framework for new hypotheses and predictions. Here we would like to extend this expectation in theories and point out that a theory can also be important when it suggests novel research *strategies*. This can be said to be true with regard to the CD-Cancer-Theory. In fact, while it may take many more years to establish causality between CD and cancer, causal links seem biologically plausible and suggestive. Please note that this appears to be true not only with regard to cancer but also with regard to many other adverse health effects.

Strategy-wise, we might now – on the basis of the CD theory – focus on protecting individuals against viable indicators of CD, i.e., against CD's short- and medium-term effects in experiments and, importantly, in human populations. The rationale being that if there are ways to prevent the putative cause or exposure we no longer have to elucidate the (possibly) many involved steps to cancer or other diseases, i.e., along the continua between health, CD exposures and diseases. This is in line with a quote from Sir Bradford Hill [1965]: "All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have ….". Indeed, sometimes we may have to act and shift emphasis early on to identify means of prevention even though we may not have conclusive and unambiguous evidence of causality in hand. This strategy approach might be even more promising in view of a series of other adverse health effects beyond such extremes as cancer which has been or will be attributed to CD, including premature ageing [Erren *et al*. 2003], depression etc. Therefore, in terms of prevention, is seems advisable to identify overt signs of CD exposures – for instance, it might be advisable to identify predisposing life-styles to prevent populations from CD as much as possible. If we were to do so and succeed there, on a short-term basis, we might be successful in preventing medium- and long-term effects of CD as well.

Conclusions

Science seeks predictability and a theory is a means to explain facts and observations in a causal and therefore predictive fashion. Since the melatonin hypothesis, a corollary and associated predictions have, as we think, examined one common theme, namely effects of CD, from very different angles and since numerous observational studies and rich experimental evidence lend objective support to the validity of the concept, we were certainly encouraged to formulate a generalized theory. Indeed, this theory unifies results of the rapid evolution of research on light, melatonin, circadian or chronodisruption, cancer and other diseases. Importantly, the theory has definitely not exhausted its potential for novel predictions.

Put differently, we generated this CD theory because, so far, the puzzle of differential cancer risks in seemingly diverse and unrelated populations such as the blind, shift-workers, flight personnel, Arctic residents and subsets of sleepers is not solved as it ought to be. But in our view, all these populations share an excess or deficit of chronodisruption which – in our theory – could explain, and would indeed predict, the observed differential outcomes.

If considered viable, the theory should be rigorously tested. If proven "right" or "suggestive", or more appropriately, if not falsified by conclusive evidence, research could proceed to identify means to avoid or alleviate CD, and its effects, to break the chain of causation which may lead to cancer, and to other disease endpoints. We are, of course, aware of the truth which the following quote holds:

> "the invention of … new theories
> regularly, and appropriately, evokes the [resistance]
> from some of the specialists on whose area of
> special competence they impinge".
> *-Thomas S. Kuhn, 1962*

And yet, the tantalizing benefit to possibly elucidate causes of epidemic breast and prostate cancers certainly warrants targeted research into the validity of the CD theory. If pursued, once again with reference to Thomas Kuhn, please note that

> "To be accepted ….
> a theory
> must seem better than its competitors,
> but it need not,
> and in fact never does,
> explain all the facts with which it can be
> confronted".
> *-Thomas S. Kuhn, 1962*

In this vein, epidemiological suggestions and experimental insights to-date could be viewed as a prelude – no less and no more – to further rigorous tests which will yield results that add to the scope and precision of the theory. Indeed, as science will strive to bring theory and present and future facts into closer agreement, the CD-Cancer-Theory can and will be modified. Ultimately, the CD-Cancer-Theory can be considered as rejected when – all or critical – predicted outcomes are negative. Alternatively, the proposed theory could be considered as "right" if – possibly after future adjustment – the "anomalous" cancer risk findings in CD-exposed populations should become the "expected".

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