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Circadian desynchrony and metabolic dysfunction; did light pollution make us fat?

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ABSTRACT

Circadian rhythms are daily oscillations in physiology and behaviour that recur with a period of 24 h, and that are entrained by the daily photoperiod. The cycle of sunrise and sunset provided a reliable time cue for many thousands of years, until the advent of artificial lighting disrupted the entrainment of human circadian rhythms to the solar photoperiod. Circadian desynchrony (CD) occurs when endogenous rhythms become misaligned with daily photoperiodic cycles, and this condition is facilitated by artificial lighting.

This review examines the hypothesis that chronic CD that has accompanied the availability of electric lighting in the developed world induces a metabolic and behavioural phenotype that is predisposed to the development of obesity. The evidence to support this hypothesis is based on epidemiological data showing coincidence between the appearance of obesity and the availability of artificial light, both geographically, and historically. This association links CD to obesity in humans, and is corroborated by experimental studies that demonstrate that CD can induce obesity and metabolic dysfunction in humans and in rodents.

This association between CD and obesity has far reaching implications for human health, lifestyle and work practices. Attention to the rhythmicity of daily sleep, exercise, work and feeding schedules could be beneficial in targeting or reversing the modern human predisposition to obesity.

Introduction

> *"It seems plausible to us that the efficiency of the cell, the overall activity of which pursues an oscillatory course, should fall when it is driven by external cycles too far removed from its evolved natural period. These external cycles might be close enough to the natural period to insure entrainment and hence synchrony of adjacent cells, but nevertheless sufficiently different from the natural period to impair coordination of the constituent intracellular processes…"* (Pittendrigh and Bruce, 1959) [1].

The preceding paragraph perhaps marks the first realisation of the potential significance of circadian rhythms for health, and the formulation of the "circadian resonance hypothesis" that states that fitness is enhanced by tight coupling of circadian rhythms to the environment. More than half a century later, evidence is accumulating to support these insightful predictions. That evidence will be examined in the following review, focusing on the evidence to support the hypothesis that such "*impaired coordination of intracellular processes*" might be implicated in an increased susceptibility to obesity.

Circadian rhythms are defined as oscillations that recur with a period approximating to 24 h, and these patterns are evident across the biological phyla. Circadian rhythms are generated by an interactive network of transcriptional and translational loops in the expression of a panel of clock genes, and this molecular "clock" is present in virtually all mammalian cells [2]. The core components of the molecular clock are remarkably conserved across evolutionary time, a testimony to their fundamental significance for life. Microarray studies have conservatively estimated that at least 10% of transcription of the mammalian genome is clock controlled [3]. Furthermore, most mammalian physiological parameters exhibit circadian rhythmicity [4], as accordingly do many human epidemiological indices such as time of birth [5] and death [6].

Circadian rhythmicity reigns across the spectrum of human life, from gene transcription in the cell nucleus, to organ function, behaviour and demography. True circadian rhythms are generated endogenously, persisting in constant conditions, yet yielding to entrainment by daily environmental cues. This facility allows animals to maintain their endogenous rhythms in synchrony with environmental conditions, with presumed adaptive advantages. The predominant environmental factor that entrains endogenous circadian rhythms is the light–dark cycle, that was until relatively recently, generated by the daily rotation of the Earth.

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Electric lighting became widely available in the early 20th century, when the role of the solar photoperiod in entraining human circadian rhythmicity became subservient, an event unprecedented over several million years of planetary history. Today, most of the developed world has complete electrification and the circadian rhythmicity of humans and many domestic animals is no longer predominantly entrained by the solar photoperiod. How naive of mankind to think that induction of chaos in this ancient and ubiquitous timing system could come without significant physiological consequence?

The hypothesis

We define chronic circadian desynchrony (CD) as the misalignment of endogenous circadian rhythms with the unpredictable daily photoperiodic cycles facilitated by electric lighting. Here we examine the hypothesis that the condition of chronic CD that has accompanied the availability of electric lighting in the developed world induces a metabolic and behavioural phenotype that is predisposed to the development of obesity and other metabolic abnormalities that affect health and lifespan. We base this hypothesis on epidemiological evidence linking desynchrony to obesity and metabolic dysfunction, in conjunction with the induction of metabolic dysfunction and obesity in desynchronised animals in controlled experiments.

The evidence

Epidemiological studies link obesity to light exposure

The World Health Organisation reported that in 2005, approximately 1.6 billion adults were overweight, and further predicted that by 2015, approximately 2.3 billion adults, or one third of the human race, will be overweight. The latest Health Survey for England (HSE) data shows that in 2008, 61% of British adults were obese or overweight, and that the proportion of obese adults had risen from 13% in 1993 to 24% in 2008 (HSE, 2010). Levels of physical activity are reported to be increasing in most age groups (Fig. 1A) in the absence of discernible effects on the prevalence of high body mass index (BMI) in the UK (Fig. 1B). Meanwhile, the trend towards increasing BMI seems unrelenting, despite a multi-million pound slimming industry, and targeting of this topic as a UK Government priority.

This inexorable trend towards increasing BMI in the developed world might be explained by a fundamental alteration in energy homeostasis so that even reduced caloric intakes are surplus to requirements, and are deposited as fat. Such a shift in metabolism and feeding behaviour could be induced by the misalignment of the light dark cycle with work, sleep and feeding rhythms, with consequent increased susceptibility to obesity.

Exposure to artificial lighting increased progressively since the availability of kerosene and gas lighting in the 1800s (Fig. 2C), culminating in a remarkable 100,000 fold increase in artificial light exposure by 2000 (Fig. 2B). Artificial lighting is the single most important factor facilitating the desynchronisation of endogenous circadian rhythms from the natural photoperiod. In support of our hypothesis, the prevalence of obesity across the developed world mirrors the availability of mains electricity (and electric light), both geographically and chronologically (Fig. 2A, B, D). Furthermore, the trend for increasing BMI among UK adult males closely paralleled the percent of households with electricity since 1920, and the percentage population that are obese per country is related to the% electrification across the globe (Fig. 2A and D). More recent epidemiological evidence implicating light exposure in the pathophysiology of metabolic dysfunction and obesity was given by a study of 5480 Finnish adults where reported levels of

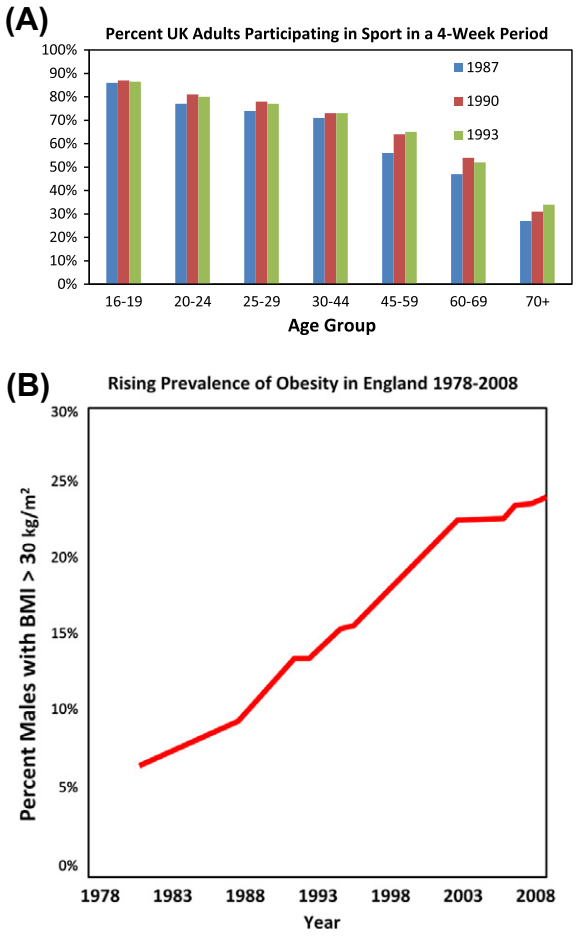

Fig. 1. Trends point towards increasing rates of physical activity, as illustrated by the percentage of UK adults that reported participation in sports over a 4-week period (UK Government General Household Survey, Ref. [57]) Meanwhile, the prevalence of obesity in the UK continues to increase (UK National Obesity Observatory, http://www.noo.org.uk).

light exposure were significantly associated with seasonal fluctuations in mood and appetite, factors that increased the risk of metabolic syndrome [7].

This striking parallel between exposure to artificial light and obesity is also graphically evident when pictures of the night sky are compared to global maps of the prevalence of obesity (Fig. 2D). Furthermore, in an intriguing example of co-adaptation, increasing rates of obesity also extend to domestic animals exposed to artificial light with recent and unprecedented levels of obesity reported in dogs, 33% [8], cats, 25% [9] and horses, 45% [10].

All of this epidemiological evidence may indicate that electric lighting is merely a good marker of developed society, which covaries with dietary and other lifestyle-related factors. Consequently, these epidemiological correlations are of very weak statistical significance, but their biological significance should be considered alongside two further key items of supportive evidence (reviewed in detail in the next two sections). Firstly, that humans exposed to acute CD develop obesity independently of other risk factors, and secondly that experimental CD induces obesity in laboratory rodents.

Acute circadian desynchrony induces obesity in humans

Chronic CD refers to small daily changes in the 24 h light:dark cycle, as induced by electric lighting, while acute CD is induced by a sudden, gross alteration of the photoperiod, as occurs during shiftwork and following transmeridian travel. There have been

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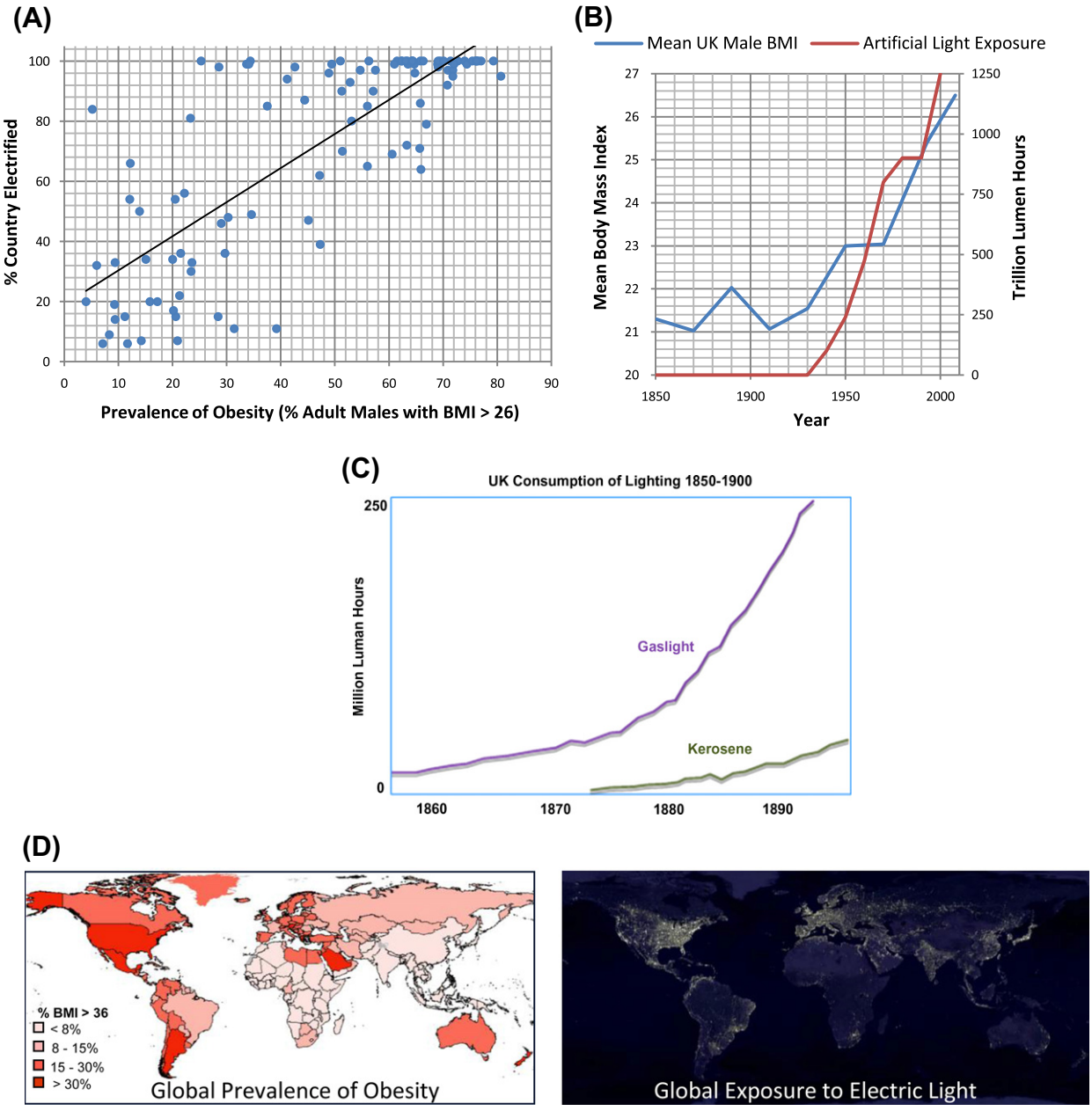

Fig. 2. Relationship between BMI and access to mains electricity in 104 countries for which data are available (Electrification Rate by Country 2007/2008, United Nations Development Programme; World Health Organisation Global Infobase). (B) The relationship between the increasing body mass index (BMI) of British adult males and exposure to artificial light over the last 150 years. (Data from Ref. [58] and [59]). A lumen hour is defined as a unit of luminous energy equal to the quantity of light radiated or received for a period of 1 hour by a flux of 1 lumen. (C) The rate of increase in BMI appears to predate increased exposure to light in (B), but the data shown in (C) demonstrate that the trend towards increased exposure to artificial light actually commenced with gas lighting, several decades earlier. (D) Geographical colocalisation between increased BMI and exposure to artificial light (WHO Infobase; Sky at Night).

no epidemiological studies of the effects of chronic CD on human health. However, in corroboration with data reported in experimental animals, human shift work was associated with weight gain, increased BMI and associated co-morbidities such as metabolic syndrome and type-2 diabetes, that were independent of lifestyle [11] and work related factors [12,13]. This finding has been reported consistently in shiftworkers from all over the world, and from various working environments including hospitals [11], offshore oil plants [14], steel industry [15], clean rooms [16], and factories [17]. A recent study examined 7254 shiftworkers over 14 years and concluded that shiftwork was a significant risk factor for obesity that was independent of age, BMI, drinking, smoking or exercise [15]. Some studies that controlled for the possibility that shiftworkers may simply have an increased energy intake have reported similar [17] or lower intakes among shift workers [18] compared to day workers. Shiftwork has also been reported to affect feeding behaviour, inducing an increased appetite for fat and fragmented eating patterns [15]. Furthermore, experimental CD disrupted glucose homeostasis in human volunteers, with several previously healthy individuals showing postprandial glucose and insulin levels that were in the range of the pre-diabetic state [19]. Such rapid induction of metabolic disruption in experimentally desynchronised humans supports the hypothesis that CD could mediate an increased susceptibility to obesity.

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There is some evidence to implicate short sleep duration in the generation of obesity in humans [20], and sleep deprivation must be considered as a confounding factor in the relationship between CD, metabolism and BMI. However, most studies implicating sleep deprivation in the obesity epidemic measured only the duration of night time sleep, and did not account for daytime sleep that could accompany disruption of circadian rhythms. It is also likely that reduced sleep duration is a consequence of obesity and its co-morbidities, rather than a direct cause of these conditions. Furthermore, it has been shown that reduced night time sleep duration in obese individuals occurred in conjunction with increased daytime sleep [21–23], a finding that suggests disruption of the sleep-wake cycle rather than simply reduced sleep duration. It is likely that complex interactions occur between sleep duration, metabolic control and CD, but the role of sleep deprivation as a primary cause of the obesity epidemic is uncertain. Reduced night time sleep duration in the obese may be an indicator of their disrupted circadian rhythms rather than a primary cause of their condition.

Experimental circadian desynchrony causes obesity in laboratory rodents

Experiments in rodents have provided considerable evidence that acute disruption of the photoperiod may be detrimental to health. Perhaps most notable among these is a study reporting the catastrophic demise (>50% mortality), of aged mice exposed to repeated experimental photoperiodic phase advance [24], when compared to age-matched unshifted mice [19]. CD also affected cardiovascular pathology in a mouse model of cardiac hypertrophy, and significantly, this effect was reversed by resumption of circadian resonance [25], thus directly implicating desynchrony in the pathophysiology of this condition. Previous studies that subjected mice or rats to CD associated these regimes with increased body weight [26–28], further suggesting that desynchronization might affect metabolism. Mice housed in photoperiods that oscillated at frequencies of 20 h gained weight and became obese compared to controls housed in the usual 24 h cycles, despite the fact that the desynchronised animals did not ingest more food [27]. Young rats showed changes in food intake and body weight that were dependent on the period of the light–dark cycle to which they were exposed, with cycles that deviated most from the animal's endogenous period associated with higher food intakes and body weight [29]. Furthermore, young mice kept in photoperiods that deviated from *tau*, had increased body weight but no evidence of increased food intake, indicating increased metabolic efficiency [30]. Finally, plasma insulin was lower in animals maintained under a 12:12 light–dark cycle, compared to animals fed the same diet in combination with CD [31]. This evidence, taken from multiple animal studies, consistently supports an association between deviation of the photoperiod from the endogenous period (*tau*) and susceptibility to increased body weight.

In accordance with the assumed adaptive functions of circadian rhythmicity, most metabolic parameters are subject to endogenous circadian control including glucose tolerance, blood glucose, feeding behaviour and feeding-related hormones [32]. Furthermore, transcription factors involved in regulation of energy homeostasis also regulate circadian timing e.g., *Pgc-1a*, [33], *Ncor1/Hdac3* [34]. It is not surprising then, that CD induced alterations in metabolic parameters in experimental animals, findings that corroborate epidemiological evidence of increased body mass in humans exposed to CD.

Animals whose endogenous rhythms (*tau*) deviate from 24 h might exist is a state of chronic CD, necessitating daily re-entrainment to the solar photoperiod. This daily re-entrainment might be similar to that required by human subjects exposed to chronic perturbation of their circadian resonance by exposure to electric light. Interestingly, we have demonstrated a significant association between the proximity of *tau* to 24 h and lifespan in all mammals for which reliable data are available [35]. These data reinforce the significance of circadian resonance, and it seems likely that deviation of *tau* from 24 h might be an evolutionary trade off tolerated in exchange for some additional adaptive mechanism. For example, animals with value of tau close to 24 h can benefit from high amplitude circadian resonance in stable 24 h photoperiods, but their circadian rhythmicity might become erratic should environmental frequencies deviate from 24 h. Conversely, animals with endogenous periods that deviate from 24 h compromise circadian resonance, but they can maintain circadian rhythmicity in photoperiods that deviate from 24 h. This reasoning is drawn from the physical properties of resonating systems that predict that an oscillator with an endogenous frequency that deviates slightly from that of the entraining frequency displays lower amplitude resonant oscillations, but maintains robust rhythmicity over a higher range of entraining frequencies. In contrast, high amplitude oscillations result when the frequencies of entraining and endogenous oscillators coincide, but this resonance is stable over smaller ranges of entraining frequencies [36].

Tau might then be considered as an evolutionary balance between the detrimental effects of CD against the inflexibility of endogenous periods that approach 24 h. Animals that exist in relatively constant environmental conditions, such as molerats that survive underground, or humans that can control their environment can perhaps tolerate values of tau close to 24 h, and benefit from the advantages of circadian resonance. At the other extreme, animals that live in unpredictable environments, encountering acute changes in [37] food availability, temperature and predation, might benefit from more responsive circadian rhythms that can reciprocate quickly with photoperiodic changes, despite the costs of CD in 24 h photoperiods.

Tau is highly heritable in birds [37], and remarkably consistent between strains of inbred mice [38], supporting the strong genetic regulation of this parameter. Deviation of *tau* from 24 h is thought to affect the ability of animals to entrain to photoperiods that do not equal 24 h, so *tau* might equally determine the capacity of some individuals to tolerate the effects of CD. Thus, susceptibility to the metabolic effects of CD might depend on the endogenous, genetically determined circadian parameters. There is also a strong genetic component to susceptibility to obesity, with relatively small shared environment effects which is surprising given the rapid expansion of this condition in recent times [39]. However, these findings are absolutely consistent with the hypothesis that the obesity epidemic arose through an interaction between an innate genetic attribute (*tau*) and a recent environment trigger (CD and electric light).

Clock gene mutant animals show disordered metabolism

In common with most areas of physiology, targeted mutations of the clock genes have provided valuable information on the physiological significance of the mechanisms they control. Many clock gene mutant animals display marked metabolic alterations which signify the fundamental role of circadian timing in regulating mammalian metabolism. For example, mice nullizygous for the gene *clock* develop obesity, and display metabolic dysfunction that is typical of metabolic syndrome in humans (e.g. hyperleptinaemia, hyperglycaemia, hypoinsulinaemia) [40]. Interestingly, polymorphisms in *clock*, which is a core component of the circadian timing mechanism, have been significantly associated with susceptibility to obesity in humans [41,42].

The *tau*-mutant hamster is an interesting model of altered circadian rhythmicity, with heterozygous animals showing free-running periods of 22 h and homozygous animals, 20 h. CD was clearly

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detrimental for the survival of the heterozygotes which developed cardiovascular and renal pathology and had a decreased lifespan when maintained in a 24 h photoperiod, but remained healthy in a 22 h photoperiod [43,44]. Such changes did not affect heterozygous *tau*-mutant hamsters kept in constant dim light, or the homozygous mutant, or animals with lesions to the master clock in the SCN, none of which are capable of entrainment to the photoperiod [43,44].

It is notable that a genetic mouse model that shows high amplitude circadian rhythms, the α-MUPA-mutant mouse, also displays a lean phenotype and attenuated senescence [45,46]. The α-MUPA mice exhibit an endogenous period that equals 24 h, which would resonate perfectly with typical laboratory lighting regimes, [47]. Intriguingly, and exactly as predicted by the circadian resonance hypothesis, these mice demonstrate attenuated ageing, low body weight, and retained youthful behaviour and appearance in senescence [45,46]. They are the antithesis of the obese desynchronised mouse. Current data cannot exclude the possibility that the phenotypic features are an effect of the mutation, and unrelated to the sustained rhythmicity and circadian resonance of the αMUPA mouse. Confirmation of these findings awaits testing of the circadian resonance hypothesis in healthy, wild-type animals, the so called *"experimental tests to which it is open"* originally proposed by Pittendrigh and Bruce in 1959, remain a glaring omission in our understanding of the biological significance of circadian rhythmicity.

The most intriguing finding of studies of desynchronised animals is primarily that exacerbated pathology and reduced health and lifespan were induced by chronic CD, but also that animals that could not entrain were consistently unaffected. This suggests that entrainment to a disordered photoperiod is a crucial component of chronic CD; unsuccessful entrainment may be less detrimental because animals default to endogenous rhythms. In support of this, life-long weekly reversal of the light dark cycle had no effect on lifespan in mice, probably because entrainment to this highly disrupted photoperiod was never properly achieved [48]. Temporal regulation may "free-run" in animals that fail to entrain, in order to maintain homeostasis until resonant environmental conditions resume.

The mechanism

Exposure to artificial light has facilitated the disintegration of the temporal architecture of human lifestyle, disrupting the entrainment of circadian rhythms to 24 h cycles and permitting activity, sleeping and feeding at times that may be physiologically inappropriate. The mechanism through which CD might affect health and lifespan most probably relates to failure of temporal coordination of physiological parameters. This failure may initiate the accumulation of macromolecular oxidative damage, and in support of this, rats subjected to acute CD showed upregulation of antioxidant enzymes [49].

Interestingly, ageing is also associated with disintegration of the circadian timekeeping system, including drifting of *tau*, reduced entrainment to light, reduced amplitude of clock gene expression and rhythm amplitude. These changes lead to desynchronization of internal circadian clocks, which probably directly contributes to the ageing process since transplantation of young SCN tissue into aged rodents restored robust rhythms and increased lifespan [43]. Furthermore, the cardiovascular changes induced by desynchrony in heterozygous *tau*-mutant hamsters (myocyte and cardiac hypertrophy, myocardial fibrosis and collagen deposition in the extracellular matrix of the myocardium [25]), are also features of normal ageing [50]. The effects of age on the circadian timing system may feature a progressive failure of synchronization between physiological oscillators producing changes in behaviour and metabolism and ultimately affecting health and lifespan. In support of this, weak circadian rhythms were strongly predictive of mortality risk in 3097 aged (mean age 84) women [51].

Photoperiod is an important modulator of physiology, and the profound changes in metabolism and feeding behaviour exhibited by seasonal animals are of particular interest. It might also be considered whether CD could induce adaptive mechanisms that are common to torpor, hibernation and short photoperiod phenotypes, which facilitate survival in harsh environmental conditions. As outlined above, CD is associated with metabolic changes that include increased blood insulin [31], increased blood leptin, fat deposition, and behavioural changes. These are all physiological changes common to other photoperiod-mediated adaptive mechanisms such as torpor, hibernation and short photoperiod phenotypes. CD may induce some form of adaptive phenotype that increases metabolic efficiency when environmental conditions become unpredictable. This type of phenotypic change could explain the refractory nature of human obesity, and resistance of this condition to dietary intervention. The phenotype of the short photoperiod hamster shares many of the features of the desynchronised animal, or human shiftworker, including changes in feeding behaviour, glucose homeostasis and body mass [52]. The mechanisms that mediate the photoperiodic regulation of phenotype in seasonal animals include structural remodelling of the brain [53,54]. Interestingly, remodelling of the hippocampus was recently reported in mice and in hamsters subjected to CD, and these neuroanatomical changes were significantly associated with behavioural changes [27,55]. Furthermore, several lines of evidence strongly implicate neuroanatomical changes such as synaptic plasticity [54], in the pathophysiology of obesity in animals, while genome wide association studies have concurrently implicated loci associated with neurogenesis and neurotrophic factors with BMI in humans [56]. Remodelling of the brain in response to an environmental trigger, such as photoperiod, could explain the refractory nature of human obesity and the resistance of this condition to dietary intervention. The disrupted photoperiod schedules imposed by electric light may trigger ancient behavioural and metabolic adaptive mechanisms that evolved to optimise survival in turbulent environmental conditions, and that now ironically, place one third of the Earth's population at risk of obesity related disorders.

The implications

The detrimental effects of CD have far-reaching implications for all aspects of human lifestyle. Resumption of the monastic lifestyle necessary for circadian resonance seems unachievable, and a more feasible intervention is the development of strategies to regulate circadian rhythmicity. For example, entrainment to scheduled time cues provided by food or exercise might maintain resonance in spite of disrupted photoperiods. It is likely that non-essential shiftwork will be curtailed in the future, and "circadian hygiene" will receive attention as a strategy for maintaining health and managing disease. If CD underlies the global increase in human body mass index, then resumption of circadian resonance could reverse this effect. This hypothesis could easily be tested by examining the interaction between desynchrony, metabolism and the response of obese animals or humans to controlled exposure to time-giving cues. The significance of circadian rhythmicity for all aspects of human physiology is becoming evident, yet we have very little understanding of the true implications of dysregulation of this system for human health. If light pollution did make us fat, then due care to the rhythmicity of daily exercise, work and feeding schedules might succeed where straightforward dietary intervention has surely failed.

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Conflict of interest

The authors have no conflicts of interest to declare.

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