Professor Russell Foster CBE, FRS

Professor Circadian Neuroscience
University of Oxford

Innovators in Healthcare Presentation

3 October 2024 online

Transcript

I'm delighted to be able to join you today. And what I'd like to talk about is lighting for human health. What we know, and perhaps more importantly, what we need to know, I thought I'd divide our time together under these three headings, give an introduction to the non-visual responses to light. It's something that I know some of you will be familiar with. Still, I want to talk about some confusing advice and mixed messaging out there about light and the way it stimulates the circadian system in particular. Then, we will end on an up-beat note, including the future and where we're going regarding dialogue and research across the sector.

Let's kick off with non-visual responses to light. Of course, the familiar function of the eye is as an image detector, either in black and white or in colour, and essentially, this IF or this image-forming for vision is something that we understand remarkably well.

By contrast, the less familiar function of the eyes, the non-imaging forming light detection or the NIF responses to light, measuring brightness, and giving information to regulate circadian, rhythm, sleep, alertness, mood cognition, pupil constriction, and of course, hormone release a whole raft of essentially non-conscious responses to light.

Now, this division in sensory tasks, the image forming and the non-image-forming is broadly, and I stress broadly, underpinned by different photo-receptors, as many of you will be aware. We showed in two back-to-back science papers a few years ago that if you eliminate the rods and the cones, then

you retain a large number of NIF, non-image-forming responses to light, such as the regulation of circadian rhythms, sleep and melatonin.

That led to the discovery of a third photoreceptor system within the eye, based upon a bunch of light-sensitive photo-sensitive retinal ganglion cells that use the blue light-sensitive photopigment, melanopsin. Let's look at the role of these photoreceptors in circadian rhythms.

And the first point I'd like to make, of course, is that what the circadian system does, is fine-tune our physiology and behaviour to the varied demands of the sleep-rest activity, the light-dark cycle.

And so we see six different parameters here that show dynamic changes across the 24-hour day, which allows the optimisation of physiology and behaviour to the varied demands of activity and rest.

The point I'm trying to make is that the circadian system delivers the right materials in the correct concentration to the right tissues at the correct time of day. And without the time structure provided by the circadian system, our biology, including our sleep, of course, is plunged into chaos.

To understand the circadian system, we have to look into the brain, into the hypothalamus. If we go to the hypothalamus and the base of the hypothalamus, we see a paired structure called the suprachiasmatic nuclei. About 100,000 cells in total in humans. And excitingly, each one of those cells contains clock genes. And once activated, of course, they produce clock proteins.

Those proteins form a complex that enters the nucleus and is degraded, so the proteins are released from the inhibition and can produce clock proteins. And then the whole cycle goes on. Essentially, what you've got is a negative feedback loop.

The result is essentially an oscillation, a 24-hour oscillation in clock protein production and degradation. That’s the essential circadian signal. But it's of no use at all. Unless this internal day, if you like, is set to the external world. And for us and most organisms, it's the light-dark cycle that provides this entrainment signal for the regulation of the clock.

And I'll come back to this in a little bit more detail in a moment. What provides that light-dark information? Well, of course, it's the photo-sensitive retinal ganglion cells that have a direct retina-hypothalamic projection from the eye into the SCN.

Now, that molecular oscillation is converted into a physiological response. The electrical activity in the SCN is low at night and has a high firing frequency during the day. Interestingly. It's the same for both a nocturnal mouse and a diurnal human. And so the decision to become nocturnal or diurnal is not as, I think, we first expected within the SCN, but it's downstream from the SCN, and what those signals are, we don't fully understand. And the final point is, of course, what we assumed is that the clock was simply driving those circadian rhythms that I illustrated earlier. And what we now know is that they're coordinating those rhythms. Every cell in the body seems to have the capacity to generate some form of circadian oscillation.

They regulate physiology and behaviour, but they're being coordinated by this master clock within the hypothalamus, the suprachiasmic nuclei. And so it's more accurate if we say the circadian system rather than the circadian clock. It's an extraordinary temporal network regulating our physiology and our behaviour.

Let's return to entrainment.

And just to emphasise what I'm talking about here, we have a light-dark cycle. And we see an oscillation in the clock, protein production, and degradation. But if we take a human and expose them to dim light, or if they are unfortunate to have no eyes and you lose that light-dark signal, then the clock continues to tick. But it becomes disconnected from the outside world.

And most of our clocks are slightly longer than 24 hours. And so we would tend to get up later and later and later, as you see illustrated with these arrows occurring later in time. The key point is that lack of entrainment, as illustrated here, gives rise to sleep and circadian rhythm disruption. That network I talked about earlier just falls into a mass of noise.

And the sorts of things that you could expect as a result of that desynchronisation of the circadian network can be seen in terms of emotional responses, fluctuations in mood or irritability, anxiety, loss of empathy, and failure to pick up those social signals from friends, colleagues, family frustration, risk-taking and impulsivity doing stupid, unreflective things.

Very important is negative salience: the tired and circadian-disrupted brain remembers negative experiences but forgets the positive ones, and you’re more likely to use stimulants such as caffeine and sedatives. And I do stress that things like alcohol or sedatives do not provide a biological mimic for sleep.

If we think about cognitive responses, the ability to multitask is the classic one.

We fail to identify what's important from all the noise that's coming in, so we can't make appropriate decisions. Memory, consolidation, attention, concentration, communication skills, and decision-making all start to fall apart.

And with long-term SCRD, as you've seen with night shift workers, their incredible disruption and disconnection from the outside world is micro-sleeps during the day, or in fact, when they're trying to drive.

One nice study on junior doctors shows that 57% after the night shift either had a crash or near-miss, increased rates of cardiovascular disease, altered stress, and lowered immunity.... probably the reason why you have higher rates of cancer metabolic abnormalities, such as type two diabetes and obesity.

Very importantly, depression and psychosis are associated with SCRD, and indeed there's evidence that poor sleep and SCRD in the middle years may be a risk factor for dementia in later years.

So it's much more than the inconvenience of feeling tired at an inappropriate time. Our whole physiology and our ability to function are disrupted due to this desynchronisation of the circadian system with environmental time.

Now, of course, this has been exacerbated because of our disconnection with environmental light exposure. In this graph here, you see from 1800 to about today, you see the shift in the time spent outdoors. Essentially in 1800, most of us were agricultural workers. Now, very few of us are agricultural workers, and estimates vary between 1 and 10% of the population that are getting very little environmental light. Most of us are in a dim, dark box inside.

How do we achieve entrainment in the urban environment? How do we compensate for this disconnect from environmental light?

The critical factors that are integrated for circadian sleep regulation in humans are outlined here. These are the sorts of factors that we need to think about: the light intensity, the duration of exposure, and individual variation. As we'll see, there are lots of differences between individuals. The wavelength or the colour of the light, the nature of the non-image-forming light detection task, the time of light exposure, whether we're young or old or male or female, those are going to have an impact. Our angle of view, our light history, and indeed the seasons. I won't have time to go through all of these, but I'll just illustrate a few of these points, and we'll kick off with light intensity.

It's worth pointing out that until 1987 and this paper from Japan by the Honmas, humans were not thought to be entrained by light outside, but it was social cues.

What the Honmas did was expose individuals to eight hours of light and 16 hours of darkness, and the light was around about 5,000 lux. And those two subjects entrained. Why didn't we think humans were light-sensitive or that light regulated the circadian system? It was because the sorts of levels of light that we use to regulate the circadian system of a mouse, within the low lux ranges was simply utterly ineffective in humans.

It takes a lot of light for a relatively long period of time. Here's a cartoon of the light levels that we experience from the 0.01 lux and the quarter moon all the way through to a hundred thousand lux, which is full, direct sunlight. If we map onto this the sensitivity ranges of the photoreceptors, we see the roads, giving us our black and white vision kick in at low light and saturate at around about 100 lux.

Our cones, providing our colour vision, kick in around about 10 lux. There's an overlap with the rods for a bit, saturating above 100,000 lux. And then finally, the photo-sensitive retinal ganglion cells, which kick in somewhere around 50 to 100 lux and and carry on being sensitive out to 100,000 lux. But this sensitivity depends upon the length of light exposure. This comparison of irradiance or intensity between the rods, codes and the PRGs is not really appropriate because it doesn't take into account light exposure duration. So the rods and cones respond within milliseconds to give us our sense of vision. But it takes many minutes, up to hours, for the PRGCs to gain sensitivity.

So let's look at light sensitivity and the duration of exposure. This is an often reproduced figure from Brown and colleagues. Here, we see an intensity range at the bottom and a response maximised to a hundred on the vertical axis. And we see threshold responses in the area of 50 to 100 lux. So that's the sort of statement that you hear that, in fact, the circadian system is sensitive to light. However, the key point is that yes, you can get a response at around 100 lux, but you need six and a half hours of light exposure to get that response. So that's a really important point.

If we think about individual variation, which is another factor we need to consider. This is a lovely paper by Phillips and colleagues; again, we're looking at melatonin suppression, and the light was for a total of five hours, four hours before bed, and then one hour in bed, and there's a 50-fold difference in sensitivities between individuals, which is remarkably broad.

If we think about the wavelength or the colour of the light. We know that those PRGCs are maximally sensitive to blue, and I'll illustrate that in a moment. However, we also know that the cones can talk to the PRGCs indirectly via cone bipolar cells. The rods again, can talk indirectly, via rod bipolar cell talking to an amacrine cell, which can then talk to the PRGCs. So, a very important point is that whilst we think of the human circadian system as being maximally sensitive to blue, and it probably is for the PRGCs, we also need to factor in the sensitivity of potential inputs from the rods and the codes. So the rods at 500, the short wavelength cone at 420 and then the two longer wavelength cones at 530 and 560. So the point is, there's a potentially broad spectral input, in fact, a very broad spectral input to the circadian system via the PRGCs and it's not necessarily additive. So Dennis Dacey and his lovely study on the Macaque monkey showed that, the short wavelength 420 cone is actually inhibitory, actually reduces the excitation of the PRGCs in response to light. So it's complicated.

We can't just assume blue.

We now know that there are five and possibly six different types, morphological types of melanopsin ganglion cells. They project to a whole range of different structures in the brain, in the hypothalamus and the thalamus, the SCN, of course, but also the ventral lateral preoptic nuclei, the lateral hypothalamus involved in sleep, but also in alertness and metabolic reward systems, the sub paraventricular zone, which is integrating circadian and metabolic information, the olivary pretectal nuclei, part of the pupil reflex. Indirectly and directly, you've got the regulation of dopamine serotonin and visual responses could be modulated by the PRGs. And of course, via the sympathetic nervous system, you have the regulation of hormone release such as pineal melatonin.

Now very importantly it's been assumed that these different responses to light all show the same sensitivities and dynamics.

And as I'll show in a minute, you can't assume this. In fact, sleep-wake behaviour has a different sensitivity to the suppression and the shifting of the melatonin rhythm. And of course, melatonin is often used as a surrogate measure for human sleep-wake behavior. The timing of light exposure is also critically important. What we see here is a cartoon of a light-dark cycle. A daily sleep pattern which is broadly aligned to the dark portion of the night. But if you get exposure to dusk, Then, what that does is delay the clock, which means the sleep-wake cycle, you'll go to bed later and get up later. The reverse is true in the morning: light advances the clock, which means you'll go to bed earlier and get up earlier. And the importance of when you see light is something we

illustrated with a study a few years ago on university students around the world. And we showed that if you sleep through the morning, as many of the students did, you don't get that morning light, so you don't get the advance. But these students were getting light in the evening around dusk. And what that did was shift the clock to a later time.

So they got the delaying portion of the light-dark cycle, but not the morning advancing portion. And what that meant is that the more evening light they got the later they went to bed. So getting light exposure at the right time is critical and needs to be factored in when we think about light as a stimulus for the circadian and sleep-wake systems.

If you think about age there are some important differences here. And I'll just talk about some of the animal work very briefly. We did a study a few years ago with young and old mice and looked at the light-induced gene induction within the SCN. And we saw that in young mice, you get big gene induction and that's half as much in the older mice. These other boxes here show the density of the retinal hypothalamic tract into the SCN is diminished in the older mice. So there's evidence from animal models that something is going on with the light input to the clock.

And that's underpinned by some studies from the Harvard group, suggesting that young adults are more sensitive to light compared to healthy older adults beyond 65 years of age. So age is going to have an impact on the sensitivity of the clock. So again, we can't necessarily extrapolate from university student studies in the lab to individuals living, for example, in the nursing home environment.

I don't have time to go into the angle of view, light history, or the seasons. But these are other factors that we need to take into consideration. Let me now, pull some of these strands together within the topic of confusing advice.

A study a few years ago now, but still very broadly cited is that eBooks damage sleep and health, this article says ‘doctors warn'. And so the approach was, during the day, individuals were maintained under dim light, 90 lux at the angle of gaze. One group was given a print book to look at with a reflectance of about one lux. The second group were the Kindle with a maximum intensity of around about 32 lux and, key point: both read for four hours between 6:00 PM and 10:00 PM on five consecutive nights and the impact of that cumulative effect of an e-book or a print book was then analyzed. Now the first point is that when you look at melatonin suppression, you see a big effect.

You see a marked melatonin suppression. And indeed, a shift in the rhythm of melatonin timing. So yes, significant impact on melatonin, suppression, and circadian timing.

BUT.... It had a very tiny effect. So basically nine minutes. So after five consecutive nights of four hours of exposure, individuals were going to sleep about nine minutes later. Now it was just statistically significant. And as one of my colleagues said at the time 'Well it may be statistically significant, but nine minutes within the scheme of things is biologically meaningless.'

And very importantly, a later study, a few years later, didn't keep individuals under 90 lux in the experiment but gave them daytime bright light exposure of around six and a half hours in the middle of the day of around 500 to 600 Lux. Now that resulted in absolutely no differences in both sleep-wake timing. So you might expect because that was a tiny effect anyway, but more importantly, melatonin levels were not affected when individuals had bright-ish light during the day.

So if we summarize that, and I think this is an important observation, there's a small impact on sleep-wake timing of looking at an eBook before bedtime. There's a significant impact on melatonin suppression and a significant impact on melatonin entrainment. But the effects on melatonin depend upon daytime light exposure. That big effect was only possible because individuals were exposed to only 90 lux prior to the experiments in the evening. So melatonin does not correlate with sleep-wake timing. It is an important point because we can't just assume, changes in the melatonin correlate to sleep-wake behavior. Melatonin and sleep timing, at different sensitivities to light, and light history, modulates evening, light or melatonin. So basically if you're sitting in dim light during the day, you're sensitizing the clock to light in the evening, I think this is a really important point.

The same is also true for computer screens. The FLux programs offer ‘night-shift’, which many of you will be aware of. Basically what these do is change a screen from a blue-enriched to a more red-enriched screen. But there's no evidence that either the FLux or the night shift, changing in spectral reflectance, is having any effect at all. There is one study, and the conclusion was night shift is not superior to using your phone without night-shift or even using no phone at all. So basically night-shift had no impact at all. And of course, there's a lot of hoo ha around these sorts of programs.

Let me wind up.

The future? I'm much more optimistic about this than you might think.

Clearly what we need to do is find out how these various factors are being integrated for the regulation of our systems, so that we can try and mimic some of this light within the the built environment. But currently, the evidence base for guidelines regarding human light exposure to optimize health is I would say inadequate and some of it I would say is misleading.

So I think we need to be careful.

We need to find out how these various parameters are working. I just want to emphasize that, of course, we shouldn't limit the studies to just the regulation of melatonin. We need objective measures of sleep by timing, which is perfectly possible. We need alertness, cognition and mood measures. We need overall well-being measures, and we need to do this in the real world. Not just with laboratory-based studies, usually on university students.

I was involved in this House of Lords Science and Technology Report last year. And I think you'll find it interesting reading. The Neglected Pollutants: The Effect of Artificial Light and Noise on Human Health. And what was so exciting, and this report went to the government, is that the government issued a statement from that report to say that the government should commission research to establish how light intensity, wavelength duration, time of exposure, light history, and age affect the circadian system.

This should move beyond the laboratory-based studies and investigate more realistic light exposure patterns for humans, which was great that they picked up on this.

And these are the people that have now taken this report to heart, COMARE, which is the committee on medical aspects of radiation in the environment.

COMARE advises on the health effects of natural and human-made radiation, both ionising and non-ionizing. And it's likely that they're going to set up a committee shortly to try and identify some of the areas where we need research and we'll recommend research to resolve some of the questions that I've introduced in this presentation.

I hope this has been useful to give a refresher on non-visual responses to light. I illustrated some of the issues with confusing advice. And I think we've got to be very careful about how we talk about light as a stimulus for the regulation of the

circadian and sleep-wake. systems. I think it can be really confusing as I articulated.

I'm optimistic about the future. I think through dialogue and research, we will get some of that missing information so that in the relatively near future, we will be able to come up with absolutely evidence-based guidelines for illuminating the built environment. So thank you for your attention.