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OPEN Impact of short wavelength light exposure on body weight, mobility, anxiety like behaviour and cytokine expression

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Mitochondria absorb short wavelengths around 420 nm. This is associated with reduced ATP and restricted mobility. The 420–450 nm range is a significant element of LED lighting and computer monitors. Here we expose freely moving mice to 420–450 nm lighting and show rapidly weight gain within a week. This may be due to reduced mitochondrial demand for circulating carbohydrates. Both groups displayed marked shifts in serum cytokines. Open field mobility was examined. The distance travelled was similar between both experimental groups and their controls. However, both experimental groups showed avoidance of central regions consistent with anxiety-like behaviours. This was significant in the 420 nm group whose wavelength exposure is closer to peak mitochondrial absorbance. These data demonstrate the potential hazards of exposure to specific short wavelengths in the visual range now common in the built environment. Data are consistent with a wider literature on systemic problems arising from exposure to short wavelength light.

Natural sunlight has a balance between long and short wavelengths and extends from approximately 300 nm to 2200 nm. Different components of this light impact on physiology. Exposure to LED light in the range of 420–450 nm, which is a strong feature of lighting in the built environment, results in a rapid and significant decrease in human blood pressure and an increase in heart rate. This is maintained for the length of the exposure. It also results in a significant decrease in vascular resistance¹. The energy levels in these exposures were within the range of natural sun light but restricted in wavelength with no longer wavelength components.

Animal studies confirm that blue light impacts on the body and that mitochondria have a spectral absorbance peaking at 420 nm². In the fly 420 nm exposure is associated with reduced mitochondrial complex activity and ATP production. It also results in mitochondrial swelling as membrane pores open and mitochondrial membrane potentials decline. These changes are associated with reduced mobility². Selective retinal exposure to 420 nm at solar environmental levels in mice produces a significant reduction and instability in retinal metabolism, lowering mitochondrial activity and shifting the balance between oxygenated and deoxygenated blood³. Here the impact of this light continued for > 1 h after the stimulus was removed. The authors suggest that this was potentially mediated by light absorption by porphyrins in the Soret band. Mitochondria are rich in porphyrin. Further, porphyrin is key in the heme production, which is part of hemoglobin that carries oxygen to organs and tissues. White LED lighting has a dominant peak between 420 and 450 nm and Wang et al. have shown that mice exposed to high intensity white LED lighting exhibit anxiety related behaviours⁴, additionally shifts in immunity and inflammatory apoptosis have been documented⁵.

While short wavelengths in the solar spectrum undermine mitochondria, longer wavelengths (650 - ~900 nm) positively influence their behaviour, increasing membrane potential and ATP production that translates into improved function in animals and humans^{6–10}. It also passively influences immunity that has declined via insult^{11,12}. Longer wavelengths have also been shown to improve systemic physiology in humans by reducing blood glucose levels due to increased mitochondria demand for sugars¹³. The mechanism of longer wavelength influence over mitochondria is different from that of short wavelength light absorption and is thought to be related by cytochrome C oxidase absorption in the mitochondrial respiration chain¹⁴.

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Although the relative influence of short and longer wavelength ranges is roughly in balance in natural sunlight, they are not in light generated from LEDs that now dominate the built environment. Here there are almost no longer wavelength above 650 nm with the light being dominated by short wavelengths with peaks commonly around 450 nm¹⁵.

Here we ask if there is a biological impact from LED generated shorter wavelengths that may undermine systemic metabolism in mice. We expose mice separately to 420–450 nm and examine a range of metrics including changes in weight, cytokine expression, mobility and anxiety-like behaviour.

Results

Body weight.

Mice exposed to 420 nm light experienced an increase in body weight over the 8-week exposure period that was significantly greater than the body weight change in control mice (Fig. 1A). When weight changes were examined on a progressive week by week basis it was clear that after 1 week of exposure significant changes were present following 420 nm exposure and weight continued to increase systematically over the 8-week period. This was not the case in the control group who experienced only relatively minor age-related weight increase (Fig. 1B).

The results of exposure to 450 nm light were largely similar to that of 420 nm exposures. There was a significant increase over the 8-week period compared to controls (Fig. 1C). On a week-by-week basis, again the pattern was similar to that found for 420 nm exposure, with a marked increase even after only 1 week of exposure (Fig. 1D). Changes in weight in both experimental groups may be due to shorter wavelengths reducing mitochondrial metabolism that in turn reduces their demand for serum carbohydrates.

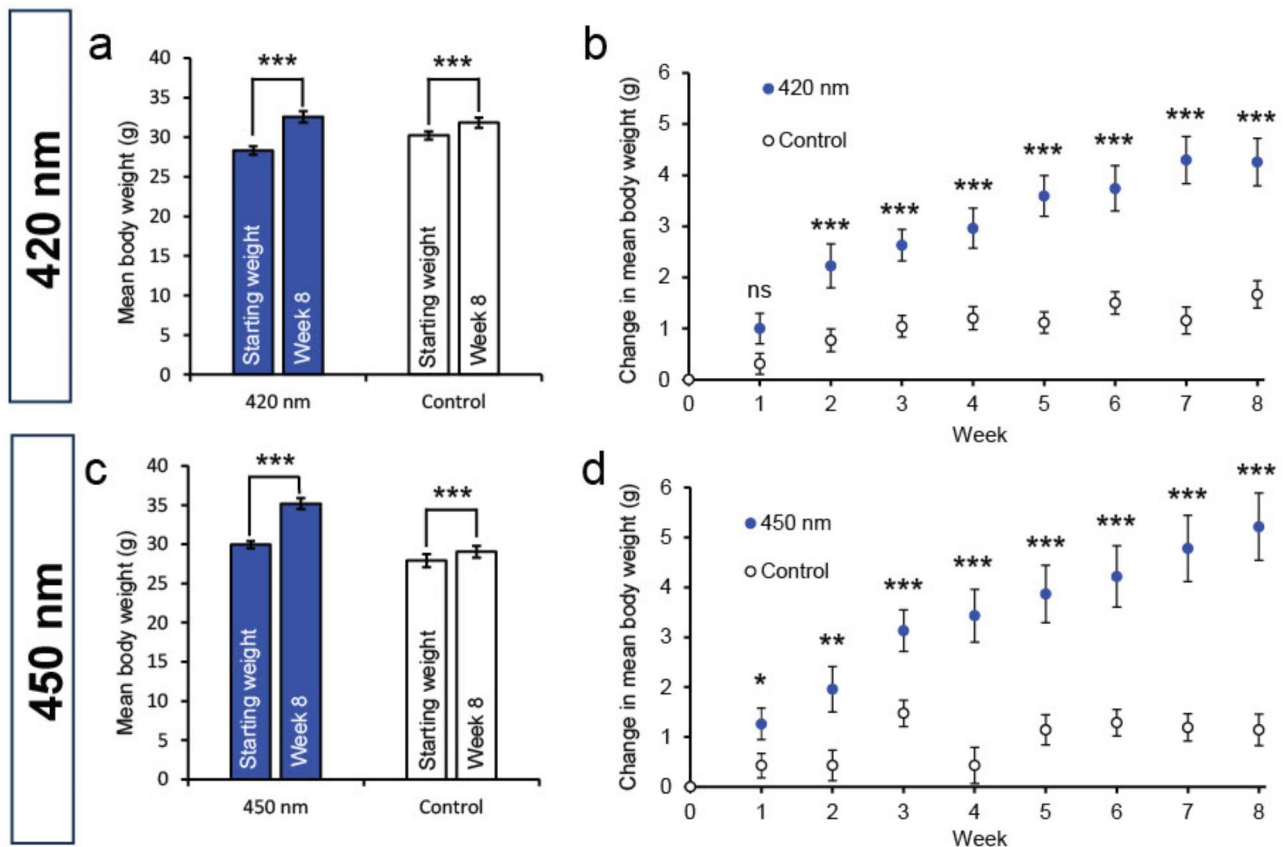


Fig. 1. Weight changes following either 420–450 nm light exposure. (A) Mice exposed to 420 nm light gained significant weight over the 8 week period, while weight gain in their controls was lower. (B) The gain in weight was progressive and apparent from week 1 and showed some levelling off at weeks 7 and 8 by which time mice had accumulated almost 3 times the weight gained by controls. At each point from week 2 the differences between controls and 420 nm exposed animals were significantly different. (C) Similar patterns were found in mice exposed to 450 nm. (D) The progressive change in weight were significantly different between exposed animals and controls at each time point. Mice exposed to light in this group accumulated approximately 4 times that accumulated in controls. In the 450 nm exposed group weight gain appeared to continue at weeks 7 and 8. Both the 420 nm and 450 nm groups are pooled data from 2 completely independent replicates with identical outcomes. Abbreviations * = $p < 0.05$, ** = $p < 0.01$, *** $p < 0.005$, ns = not significant.

Serum cytokines

It has previously been demonstrated that long wavelength exposure (670 nm) delivered via environmental lighting in mice significantly shift cytokine expression in serum. However, changes were complex and taken as a measure of the systemic impact of the light¹² as there were no obvious patterns in the changes.

Complex changes in serum cytokines were demonstrated here following exposure to 420 nm light (Fig. 2A-C) that were similar to those found following exposure to 450 nm light (Fig. 3A-C). In both cases overall patterns were similar. Both figures give the shift in the overall expression patterns (A and B) followed by graphic representation of those changes that were >two-fold in the light treated group (C). As with previous studies that have mapped cytokine shifts following differential light exposure, changes are complex¹². The key point of demonstrating shifts in cytokines in serums is that they confirm that light-induced changes can have systemic impact.

Mobility

Light exposure to long or short wavelengths impacts on mobility in insects with longer wavelength (670 nm) improving mobility in aged flies⁶ and shorter wavelengths (420 nm) reducing mobility². Here mice exposed to the two different short wavelengths were monitored in an open field environment and their movements recorded at 4 and 8 weeks of light exposure.

Exposure to 420 nm had no impact on the total distance travelled in the test arena against controls either at 4 or 8 weeks. (Fig. 4A and G). However, there were significant differences in the regions they occupied. At 4 weeks mice travelled a significantly shorter distance and spent less time in the central zone with corresponding increases in the peripheral zone (Fig. 4B, C, D and E). This pattern is clear in the open field map summary (Fig. 4F). At 8 weeks a similar pattern was found (Fig. 4G, H, I J and K). Again, this is clear in the overall field summary pattern (Fig. 4L). However, although these mice tended to spend more time in the periphery than the centre, this did not reach statistical significance.

Similar patterns at the two time points were apparent in mice exposed to 450 nm (Fig. 5). However, none of the metrics at either 4 or 8 weeks reached statistical significance. Differences between the impact of the two

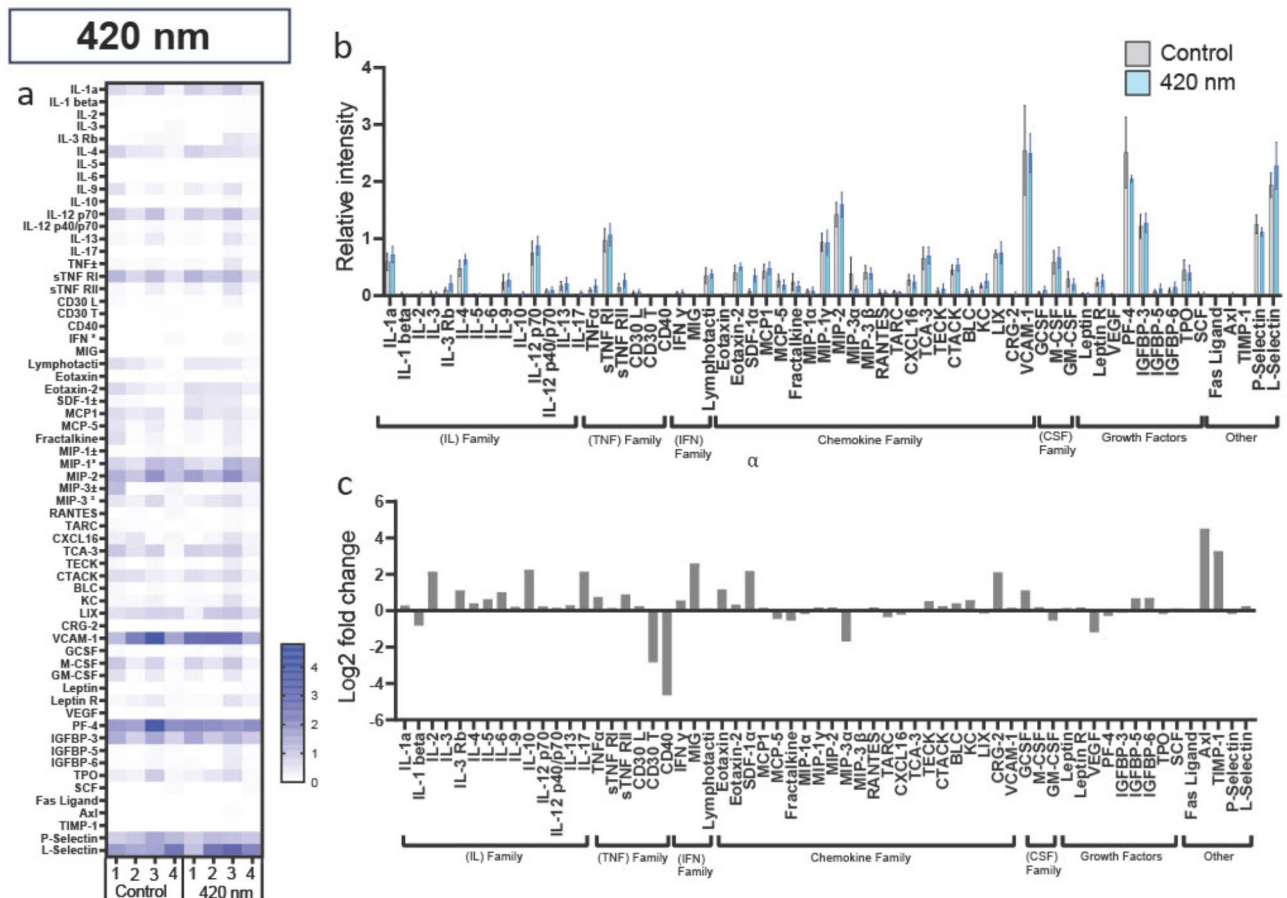


Fig. 2. Cytokine arrays from serum in mice exposed to 420 nm light for 8 weeks. (A) heat map shifts between experimental and control groups (B). Shifts in individual cytokines and (C). changes that were greater than 2-fold in the 420 nm group vs control. 420nm exposure results in complex cytokine shifts in the serum. These data show that 420nm light exposure results in systemic cytokine changes that may act to signal the impact of light exposure across the body. Error bars are SEM

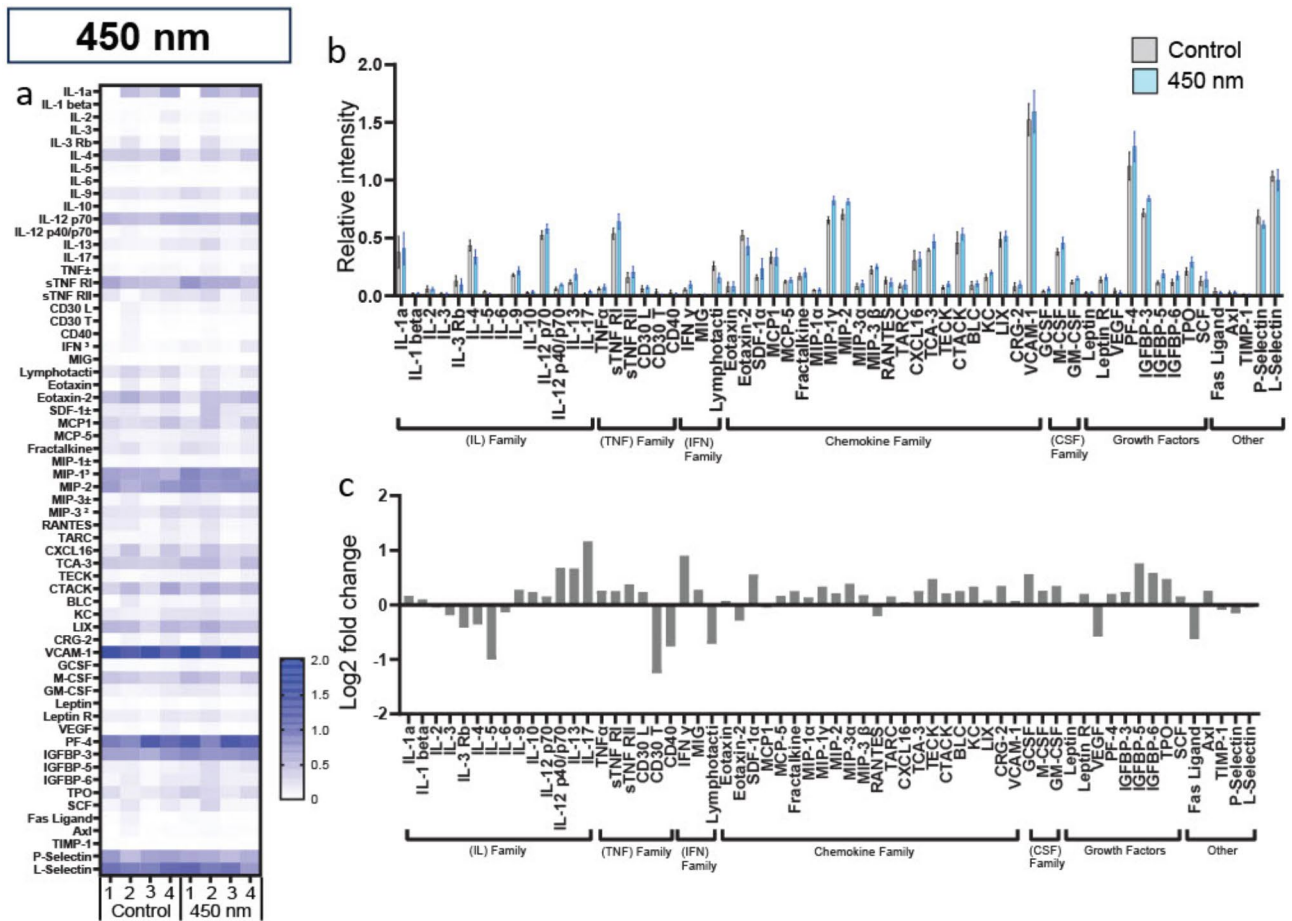


Fig. 3. Cytokine arrays from serum in mice exposed to 450 nm light for 8 weeks. (A) heat map shifts between experimental and control groups (B). Shifts in individual cytokines and (C) changes that were greater than 2-fold in the 450 nm group vs control. 450 nm exposure results in complex cytokine shifts in the serum. These data show that 450nm light exposure results in systemic cytokine changes that may act to signal the impact of light exposure across the body. Error bars are SEM

wavelength exposures on mobility may be a consequence of the 420 nm exposure being closer to the maximum absorbance of mitochondria and hence greater impact on mitochondrial integrity.

Discussion

This study reveals that two short wavelengths present in the human and mouse visual ranges, 420 and 450 nm both generated by LEDs and common in the built environment have significant detrimental impact on mice. Critically, exposure to these wavelengths result in significant and rapid increases in body weight above that in controls. Over the 8-week period controls put on approximately 1 g in weight while experimental animals put on an average of approximately 5 g. An unexpected feature of this weight gain was its rapid development with differences between experimental and controls apparent after just one week.

In bees 420 nm light dysregulates blood sugars resulting in their elevation in a standard blood glucose tolerance test, while 670 nm significantly improves glucose tolerance. Glucose was not monitored in this study, but in light of previous work it is possible that 420 nm and 450 nm both reduced mitochondrial function resulting in reduced demand for serum glucose¹⁶. Although similar experiments have not been undertaken in humans, it is established that 670 nm light that increases mitochondrial activity results in increased oxygen consumption and tighter regulation of serum glucose¹³. While short wavelength exposure has a significant and very rapid impact on human physiology, particularly heart rate and blood pressure¹, but it remains unknown if this includes blood glucose regulation.

These data are of importance in a wider human context. Reduced control of blood sugars and progression towards diabetes is a growing concern in the Western world. Such concerns sit within a world in which artificial lighting in the built environment has shifted towards use of LEDs that have almost no energy above 650 nm but often strong peaks in the 420–450 nm range. This maybe a matter of concern for public health.

The short wavelength exposures changed serum cytokine expression in both 420 nm and 450 nm exposed animals in roughly similar ways. The changes in each are likely to be interdependent and complex and no attempt is made here in their analysis due to these complexities. This is similar to previous complex cytokine changes

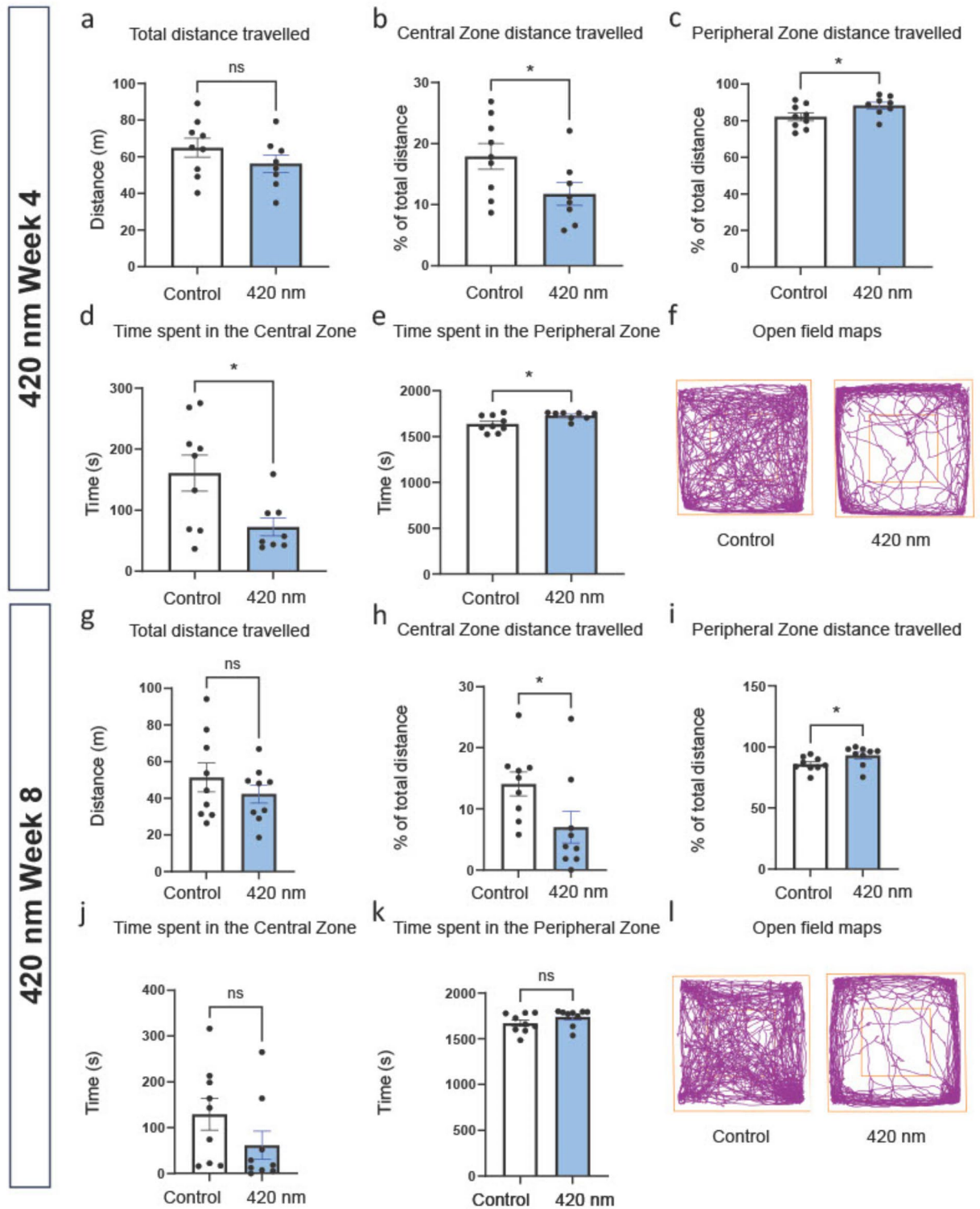


Fig. 4. Mobility of mice exposed to 420nm light and their controls at 4 (A-F) and 8 weeks (G-L). After 4 weeks of exposure there was no difference in the total distance travelled between experimental and control mice (A). But there were differences in the distance travelled in central and peripheral regions of the open field with significant reductions in time and distance travelled in the centre in favour of the periphery (B, C, D and F). This is clearly shown in the open field map (F). Overall results are similar at 8 weeks (G, H, I, J, K and L). However, some data sets did not reach statistical significance although their trend was clear (G, J and K). Again, differential patterns are clear in the open field map (L). Error bars are SEM. Statistical abbreviation * = $P < 0.05$, ns = not significant

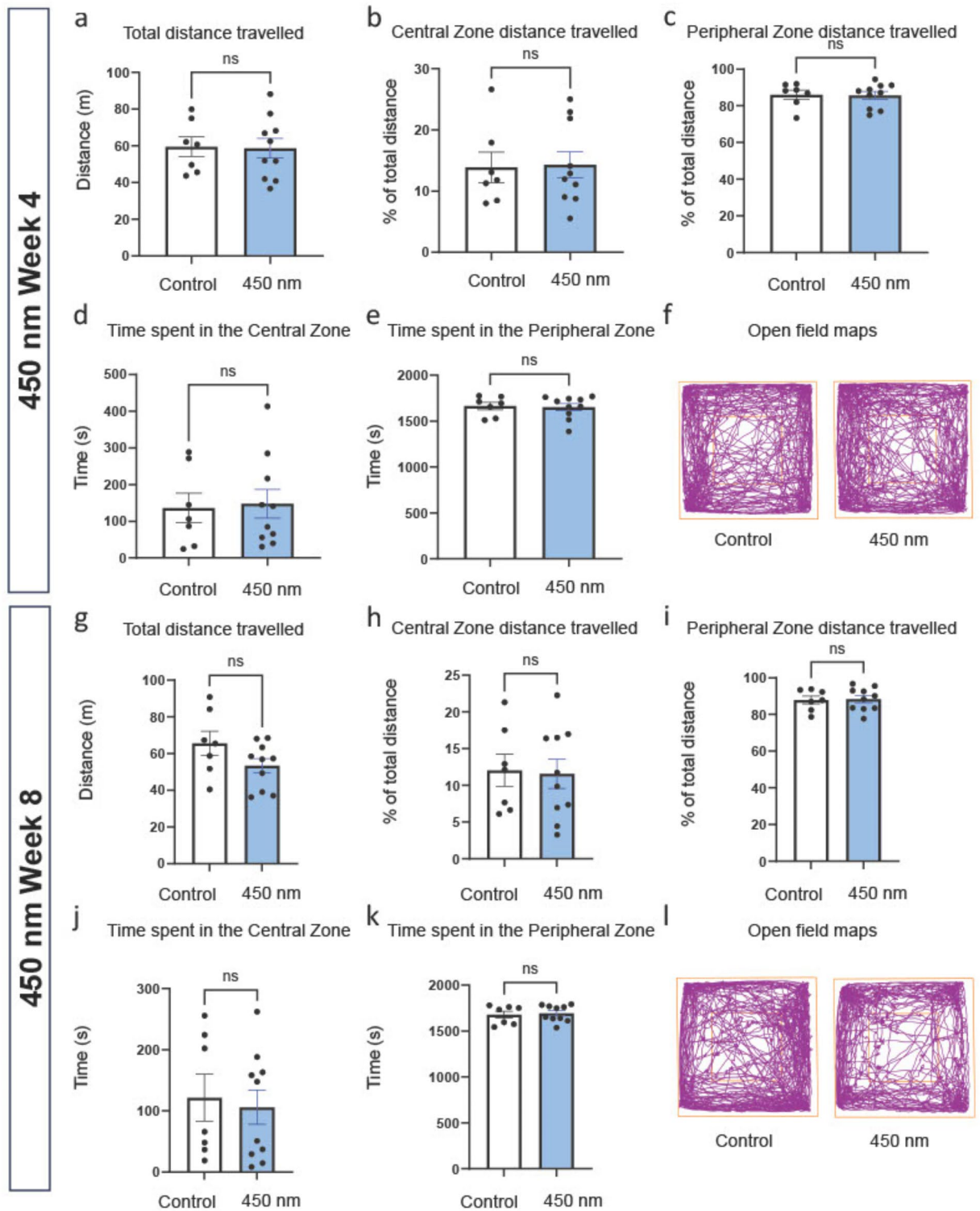


Fig. 5. Mobility of mice exposed to 450 nm light and their controls at 4 (A-F) and 8 weeks (G-L). After 4 weeks of exposure there was no difference in any of the metrics measured in the open field. These are clearly represented in the overall field map (F) Similar patterns are seen at 8 weeks with no statistical differences between experimental and control mice in the open field (G, H, I, J K and L). However, the total distance travelled between experimental and control mice was reduced in experimental animals. This can be seen in a greater thinning in the 450 nm central regions of L compared to control. Hence while 420 nm has a marked impact on open field behaviour 420 nm does not. Error bars are SEM. Statistical abbreviation ns = not significant

following long wavelength light exposure¹². But the important point is that cytokines do change as this may act as a signal across the body. Inflammatory cytokines have shown to disrupt insulin and leptin signalling, leading to insulin resistance, leptin resistance, increased fat storage, overeating, and weight gain in a self-perpetuating cycle¹⁷.

Light penetration of tissue *in vivo* is wavelength dependent. Short wavelengths such as those used here are unlikely to penetrate beyond the skin, while longer wavelength will penetrate deep into the body. Consequently, 420 nm and 450 nm are probably only absorbed by the skin, but this absorption likely sets up cytokine changes that run throughout the body including its deeper regions. Hence, it is possible that cytokine shifts induced by light represents a form of communication influencing all tissues. This remains a largely unexplored feature of light exposure that may impact on general physiology.

Flies exposed to 420 nm have reduced mitochondrial complex activity and ATP production. Also, their mobility is reduced². But mice exposed to shorter wavelengths here did not have reduced mobility. Rather, those exposed to either wavelength had similar mobility to controls. The only difference was that light exposed mice showed a reluctance to occupy the central area of the open field. This is a common feature of anxiety-like behaviour¹⁸.

Short wavelength light can be proinflammatory increasing reactive oxygen species^{19–23} and inflammation can drive anxiety, depression and stress^{24–26}. This may be the explanation why mice exposed to short wavelength light avoided central open field locations as they were experiencing light induced inflammation that was translated to anxiety-like behaviour.

The results of this study offer cautionary data to the potential health risks of short wavelength light that now dominates the built environment. However, any research in this area will suffer from significant limitations because there are too many variables. Known variables include light wavelength, its energy, the integration of energy over time, the age and health status of those exposed to light along with others that at present remain unclear. In spite of this, the key finding of this study regarding the changes in body weight in response to short wavelength light is a major concern in that is a potential matter for public health.

Methods

Experimental paradigm

Mice were exposed to either 420–450 nm light with independent controls and the impact of this on a range of physiological metrics were assessed. These included weight, serum cytokines and mobility. There were equal numbers of experimental and control mice in each group. Controls were maintained in the same manner as experimental animals but were not exposed to either of the short wavelengths. Each experiment was independently replicated sequentially with a different group of mice of the same number and age. All experiments were conducted in accordance with the regulations of Kuwait University (Animal Resources Centre) and ARRIVE guidelines. The protocol was reviewed and approved by Animal Ethical Committee of the College of Medicine, Health Sciences Centre, Kuwait University, Kuwait, 13,110.

Animals

A total of 97 male C57bl mice (The Jackson Laboratory, USA) were used at 6 months of age. Mice were divided equally between experimental and control groups in two separate replicates. Siblings were kept in the same cages. The experimental procedures exposing animals to short wavelength light had a duration of 8 week. Mice were housed in standard conditions with a 12/12 light cycle with free access to standard mouse feed and water. Food intake was not monitored; however, we appreciate that this should be undertaken in future studies of this nature. Animal house rooms were illuminated with Osram L36W/765 cool daylight fluorescent strip lights in units of 3. There were 2 units per room. Experimental and control animals were kept in separate rooms under the same room lighting conditions.

Short wave lighting exposure

Experimental animals were exposed to a light source of 20 for 420 nm and 24 for 450 nm regularly spaced LEDs mounted on an aluminium plate PCB Board measuring 14.5 × 10.6 cm and 10.7 × 8.2 cm respectively placed above the cage tops. LEDs were lensed with a 90 Degree output angle. Two different LED boards were used. One with a peak output of 420 nm and the other with a peak output of 450 nm. The half power band width of each was approximately 14 nm. Hence, any overlap between the spectral output of the two LED sets was below that half power bandwidth of each. The energy generated by each was balanced at approximately 13mW/cm² at cage floor level for both light sources and exposures were for 5 h per day from 11am to 4pm during the day time of the 12/12 light to dark cycles. Each week mice were examined and weighed. A 2-way ANOVA with post-hoc T-test was used to compare control and experimental groups.

Open field mobility testing

This was determined prior to light exposure, at 4 weeks halfway through the exposure period and at 8 weeks prior to sacrifice. Each mouse was placed in the corner of a sound insulated open field box (W × L × D = 50cm × 50cm × 50cm) with a digital camera oriented above connected to a PC with a video-tracking system (ANY-Maze, Stoelting Co, IL, USA), which records movements. A centre zone was defined as a square 12.5 cm apart from the wall²⁷.

Mice were moved to the experimental room and were acclimatized to room conditions for 1 h before being introduced into the chamber. Prior and post testing of each animal, the open field chamber was cleaned with 70% ethanol and dried. Mice were allowed to move freely in the novel environment for 30 min while their movements were recorded. The distance travelled and time spent in the peripheral and central zone were assessed. Number of mice tested in open field were 9 experimental and 9 control in the 420 nm experiment and 10 experimental

and 7 control in the 450 nm experiment. For statistical analysis, Student's t-test was used. GraphPad Prism (v 10.1.0).

Blood serum collection

Mice were killed by cervical dislocation at the end of the experimental period and blood was collected by cardiac puncture using 1 ml 27G needle. Blood was allowed to clot on ice for approximately 20 min. Centrifuged at 2000 x g for 15 min in a refrigerated centrifuge. The serum was collected and stored in -80 °C until used for the cytokine assay. Protein concentrations were quantified by an Epoch™ Microplate Spectrophotometer (BioTek Instruments, Inc., Winooski, VT, USA).

Cytokine antibody array

Mouse cytokine antibody array (Abcam, Cat# ab133995) was used to evaluate the levels of 62 different cytokines in serum samples²⁸. 4 samples from Control and LED treated group from both 420 nm and 450 nm were used. The membrane was incubated with the serum, washed, and incubated with biotin-conjugated secondary antibody and horseradish peroxidase-conjugated streptavidin. The membranes were washed and stained with kit luminol reagent and exposed to photographic films. Developed films were scanned and ImageJ used to quantify signal densities, which were normalized to the background on the membrane. Protein expression was expressed as a percentage density of positive control. Normalized signal density of each cytokine in each sample was used to plot the heatmaps. Obese to lean expression ratios were calculated, and values that showed more or less than a two-fold change were considered significant. GraphPad Prism (v 10.1.0).

Data availability

The authors declare that all data associated with the current study are available from the corresponding author upon request.

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Author contributions

All authors have read and approved the final version of the manuscript. The authors declare no conflict of interest and author contributions were as follow; HA-H: conceptualization, investigation, formal analysis, writing original draft, writing review editing, funding acquisition; MA-O: investigation, formal analysis, review and editing BA: investigation, formal analysis, review; MP: formal analysis, writing, review and editing; SH: investigation, formal analysis, review and editing; GJ: investigation, formal analysis, writing review and editing.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

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