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RESEARCH ARTICLE

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Light stimulation of mitochondria reduces blood glucose levels

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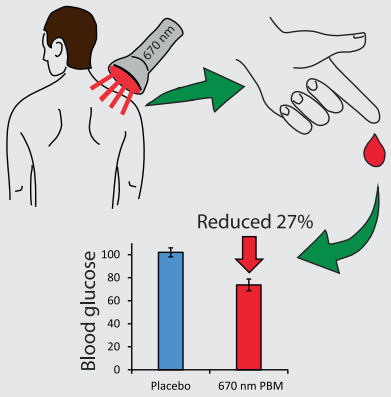
Abstract



Mitochondria regulate metabolism, but solar light influences its rate. Photobiomodulation (PBM) with red light (670 nm) increases mitochondrial membrane potentials and adenosine triphosphate production and may increase glucose demand. Here we show, with a glucose tolerance test, that PBM of normal subjects significantly reduces blood sugar levels. A 15 min exposure to 670 nm light reduced the degree of blood glucose elevation following glucose intake by 27.7%, integrated over 2 h after the glucose challenge. Maximum glucose spiking was reduced by 7.5%. Consequently, PBM with 670 nm light can be used to reduce blood glucose spikes following meals. This intervention may reduce damaging fluctuations of blood glucose on the body.

KEYWORDS

670 nm, glucose, human, mitochondria, oral glucose tolerance test, photobiomodulation, red light

1 | INTRODUCTION

Mitochondria provide the energy for cellular metabolism, using oxygen and glucose to produce the energy-rich nucleoside adenosine triphosphate (ATP). Their production of ATP declines with age and disease. It is established that photobiomodulation (PBM) with long wavelength light between ~650 and 900 nm spanning the visible through to the near infrared range, upregulates mitochondrial production of ATP and also reduces reactive oxygen species [1–5]. This upregulation by PBM is conserved across species and animal kingdoms [6–9].

Longer wavelength light is absorbed by cytochrome C oxidase in the mitochondrial electron transport chain. This leads to an increase in electron transport activity that increases mitochondrial membrane potential and ATP production [10]. There is also evidence that long wavelengths reduce the viscosity of nanowater surrounding rotary ATP pumps improving their efficiency [11].

A 670 nm PBM-induced upregulation of the production of ATP by mitochondria is marked in aged or challenged systems where ATP production has declined [4, 5, 12]. It is also more demonstrable in regions of high metabolic activity such as the central nervous system (CNS). Consequently, ATP that has declined through ageing can be improved by ~30% in whole flies [13] and 15% in mouse retina and ~50% in mouse brain [5].

Single exposures to 670 nm light can be effective within 3 h and can have impact for up to 5–7 days [8]. Critically, these improvements result in significant changes in serum cytokine signalling that is transmitted across the body [14]. This may be mediating the abscopal effect [15]. This effect is established in cancer treatment where specific irradiation of a primary tumour can result in shrinkage of distally located secondary tumours. Likewise, 670 nm PBM selectively to the back of mice has been shown to result in improvements in a model of Parkinson's disease [16] and in the retina in a mouse model of diabetic retinopathy [17].

Improvements in ATP production have been shown to translate into positive shifts in function. This includes mobility and range of sensory and cognitive abilities in flies [9], and improved visual ability in both animal models and humans [8, 18]. The widespread generality of these effects arises because membrane pumps in cells in the CNS consume large quantities of ATP to maintain normal function irrespective of the modality.

A 670 nm PBM has been demonstrated to improve mitochondrial respiration with systemic consequences, and that increased ATP production will demand increased glucose consumption. Hence, we test the hypotheses that this may be detectable in changes in plasma glucose levels. Evidence in favour of this hypothesis comes from the finding that light can regulate circulating glucose concentrations in insects [19]. We address this hypothesis by examining the effect that 670 nm PBM has upon human circulating plasma glucose levels over the course of a standard oral glucose tolerance test.

2 | METHODS

2.1 | Study cohort

This study was approved by City, University of London, School of Health and Psychological Sciences Research Ethics committee (*ETH2122-1596*). We confirm that all research was performed in accordance with relevant guidelines/regulations, and that all participants gave informed consent to take part. This study was performed in accordance with the Declaration of Helsinki. Thirty healthy participants were recruited: 15 in the 670 nm PBM group (mean age 41.1 ± 13.1 years), 15 in the placebo group (no light; mean age 38.3 ± 13.7 years). They had no known metabolic conditions and were not taking medication. Adiposity influences glucose metabolism, body mass index was not taken for each participant; as such adiposity could not be taken into account during analysis.

2.2 | Study protocol

Participants were randomised into either a 670 nm PBM group, or placebo (no light) group at the point of recruitment. All individuals undertook two fasting oral glucose tolerance tests (OGTT) over a 7-day period, each time consuming 75 g glucose in 150 mL of water. Capillary blood glucose levels were recorded by finger prick tests, and respired end-tidal carbon dioxide partial pressure ($EtCO_2$) were measured every 15 min for 2 h while at rest. For all individuals in both groups, an initial control OGTT was recorded during their first visit (Figure 1A).

Within 7 days, a second OGTT was administered during which the 670 nm PBM group received a 15 min 670 nm light exposure 45 min prior to consuming glucose. Participants in the placebo group were positioned identically for 15 min but the 670 nm light was not turned on (Figure 1A). Energies and timings of lights are consistent with previous studies [12].

Three comparisons were made between OGTTs for analysis (Figure 1B). Comparison 1: The 670 nm PBM and placebo intervention results were compared. To confirm that findings from cross-group comparisons are not due to marked variability between individual responses [20], paired-participant analysis was also carried out. Control OGTT response data from individuals (obtained on visit 1) were compared against the OGTT response data from the same individuals following an intervention (visit 2). Comparison 2: paired-participant analysis, within 670 nm PBM group, Comparison 3: paired-participant analysis, within placebo group. Additionally, given the known variability in response to the OGTT between individuals, we validated any significant differences by also conducting a within subject before and after paired analysis. This paired analysis reports changes with individuals, between a visit in which no intervention was conducted, with a second visit, during which they had the intervention (placebo or 670 nm light exposure). A 670 nm PBM is reported to have protracted effects lasting ∼5–7 days following a single exposure [8]. It is also reported that an individual's OGTT response curve varies over extended periods of time [21]. Hence, a crossover study design was not undertaken to avoid the impact of these unknown variables.

2.3 | Oral glucose tolerance test and blood glucose monitoring

Participants fasted overnight, consuming only water for at least 10 h prior to the OGTT. An initial finger prick capillary blood glucose level was measured using a blood

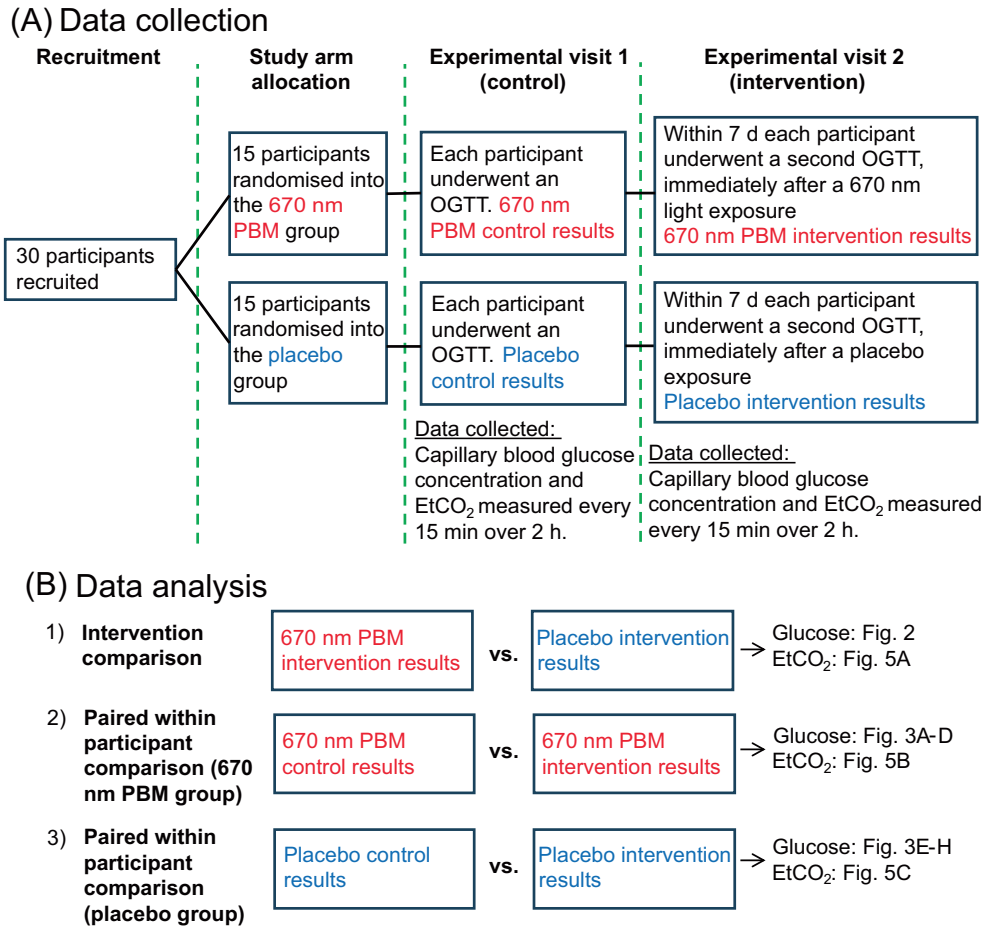


FIGURE 1 Study protocol and data analysis design. Study protocol flow diagram (A) and data analysis overview (B). (A) Thirty participants were randomly assigned into each arm of the study, 670 nm photobiomodulation (PBM) group or placebo group. Each participant came in for two visits. During the first visit, they underwent a fasting oral glucose tolerance test (OGTT), during which circulating blood glucose concentration and end end-tidal CO_2 ($EtCO_2$) were measured. Within 7 days they returned for a second visit, during which they were first exposed to an intervention, either 670 nm PBM (670 nm PBM group) or no light exposure (placebo group), following which a second OGTT was conducted and blood glucose/$EtCO_2$ data collected. (B) Data were analysed in three comparison sets. Comparing first the two intervention data sets from visit 2, such to determine statistical differences in intervention types and rule out a placebo effect (B_1). To limit the risk of false positive results from this comparison, due to variations in individuals OGTT responses, each participants data was compared against the control results taken during visit 1, a paired participant analysis was performed (B_2, B_3). Included in (B) are figure number links to the results from each comparison, for circulating blood glucose (Glucose) and $EtCO_2$.

glucose monitor (Kinetik Wellbeing, UK), which has demonstrable sensitivity [22]. Subsequently, participants consumed 75 g glucose in water (total volume of 150 mL), within 2 min. Following glucose consumption, further finger prick blood glucose concentrations were measured at 0 (fasted), 15, 30, 45, 60, 75, 90, 105, and 120 min.

2.4 | Respiratory measurements

End-tidal expired partial pressure of carbon dioxide ($EtCO_2$) and breath rate was measured at the same time intervals as blood glucose. This was via capnometry, using a PC-900B Handheld SideStream $EtCO_2$ monitor (PROACT medical, UK), and nasal cannula.

2.5 | Light exposure

During the participants second visit an intervention was undertaken prior to OGTT measurement. In the 670 nm PBM group, immediately following initial blood glucose measurement, participants exposed an 800 cm^2 region of upper back to 670 nm light for 15 min at an intensity of 40 mW cm^{-2} (28 800 J). This would illuminate skin cells and underlying musculature including the trapezius [23]. Light was delivered via light emitting diodes (LED); 670 nm peak wavelength with a half power band of ~10 nm (Light Power Health, UK). The LED array was positioned 400 mm from the participants back, surrounded by a shield that rested on the participant's skin, to prevent light leakage, and to blind the participant to

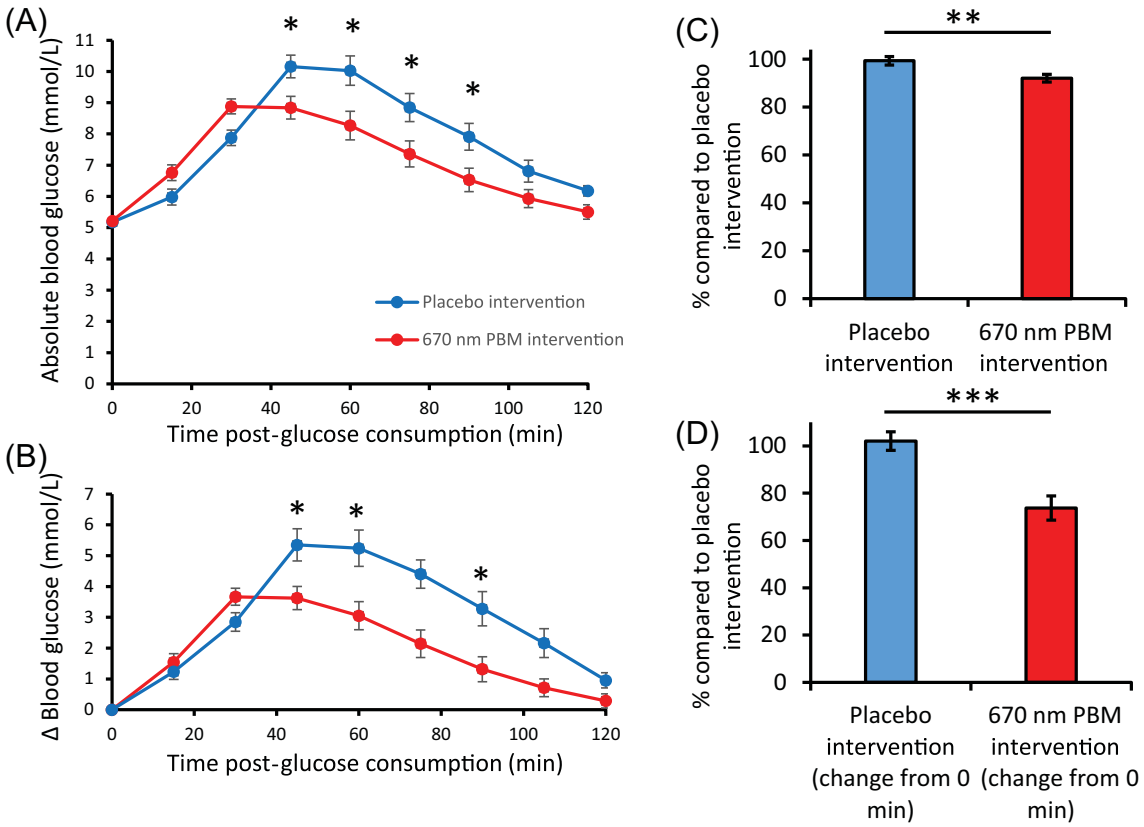


FIGURE 2 A 670 nm photobiomodulation (PBM) reduces blood glucose levels. Exposure to 15 min of 670 nm light ($n = 15$), starting 45 min prior to oral glucose tolerance test (OGTT), significantly reduced blood glucose levels, from time point +45 min, compared with a placebo intervention (no light, $n = 15$). This was observed when the absolute blood glucose concentrations were compared (A) and confirmed by analysing each participants change in blood glucose from time point 0 min (B). Area under the curve analysis shows a 7.3% reduction in total circulating glucose concentration (C, $p = 0.0061$), and a 27.7% reduction in the post-glucose consumption rise in glucose levels (D, $p = 0.0002$) $^*p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.005$. Error bars are standard error of the mean.

which group they were randomised into. The placebo group underwent the same procedure, except the LED array was not switched on during their placebo intervention.

2.6 | Statistical analysis

Due to the variation in initial circulating blood glucose concentration and $EtCO_2$ partial pressures between participants, the deviation from initial measurement at 0 min (fasting) was used for analysis along with absolute values. Circulating glucose concentration in the blood over the 2 h OGTT was determined by measuring the area under the curve of circulating blood glucose over time. This was carried out assuming linearity between data points at sequential time intervals. For comparison between the intervention results of the two groups (670 nm PBM vs. placebo), each intervention was first baselined against that groups control OGTT data and expressed relative to this for each participant. A repeated measures analysis of variance (MANOVA) using a general linear model with repeat measures, with post hoc Mann-Whitney *U* test was used to test for significant difference. A post hoc Wilcoxon Signed Rank Test was used for paired data analysis comparing intra-participant data (two-tailed tests in each case, SPSS v25). Standard error of the mean was calculated for error bars. Group age ranges are reported with standard deviations.

3 | RESULTS

3.1 | Effect of red light on blood glucose parameters

OGTT data were similar over the first 30 min following glucose consumption in the 670 nm PBM and placebo groups irrespective of whether data were generated from absolute levels, or when baselined against time point 0 min (Figure 2A,B). Baselining data against time

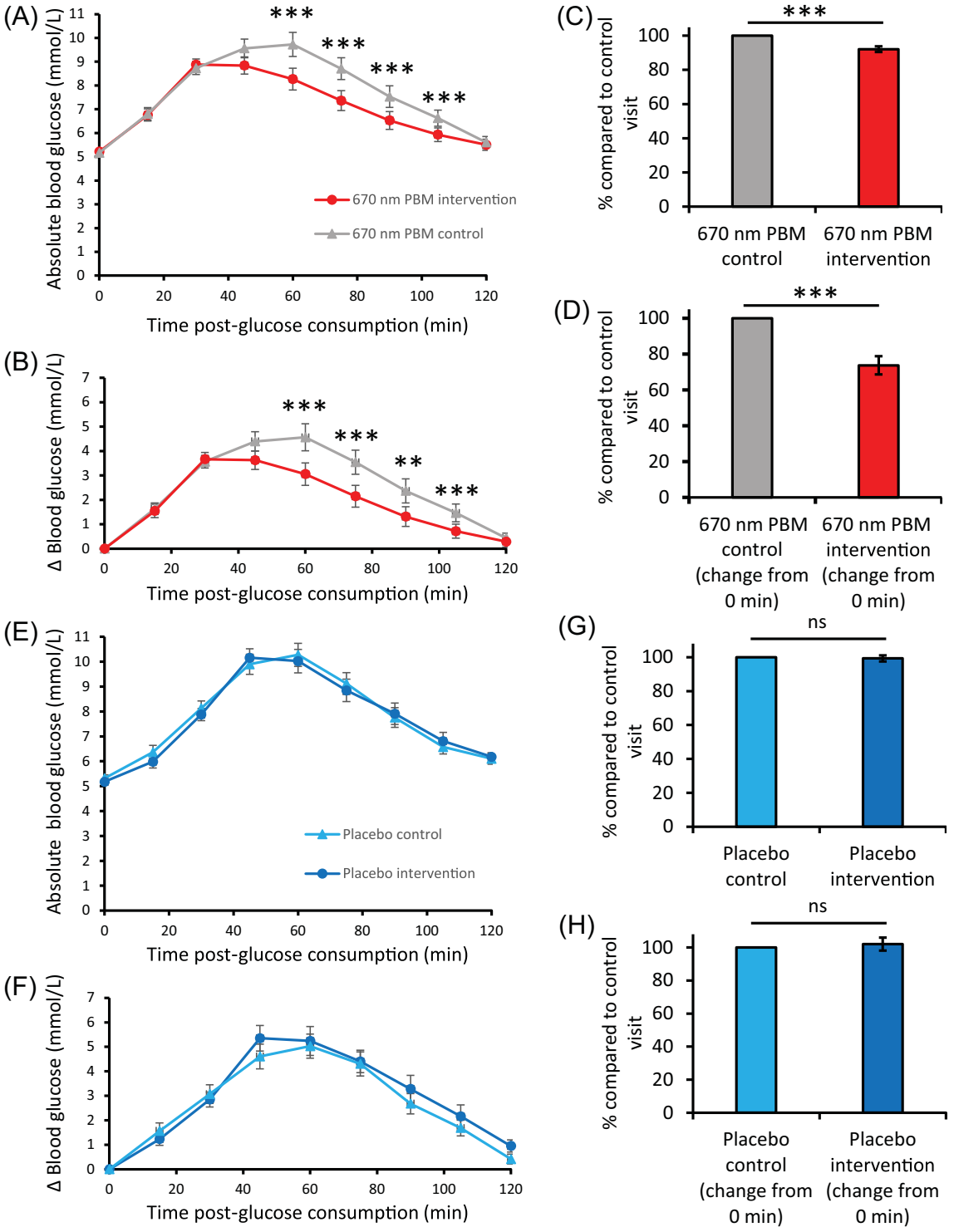


FIGURE 3 A 670 nm photobiomodulation (PBM) alters the oral glucose tolerance test response within individuals. Paired participant analysis, comparing individuals oral glucose tolerance test (OGTT) responses before and after PBM (A–D). A 670 nm PBM reduced the absolute blood glucose concentration (A) and blood deviation from time point 0 min of the OGTT (B), in individuals. Area under the curve analysis showed a 7.9% reduction in total blood glucose concentration during the OGTT following PBM (C, $p = 0.0012$), which results in a 26.3% reduction in post-consumption deviation (D, $p = 0.0008$). (E–H) Glucose response within a single population was carried out as above for the placebo intervention; there were no significant differences found, when comparing absolute blood glucose concentration, or analysis of change from 0 min of the OGTT. ***$p < 0.005$, ns, not significant. Error bars are standard error of the mean.

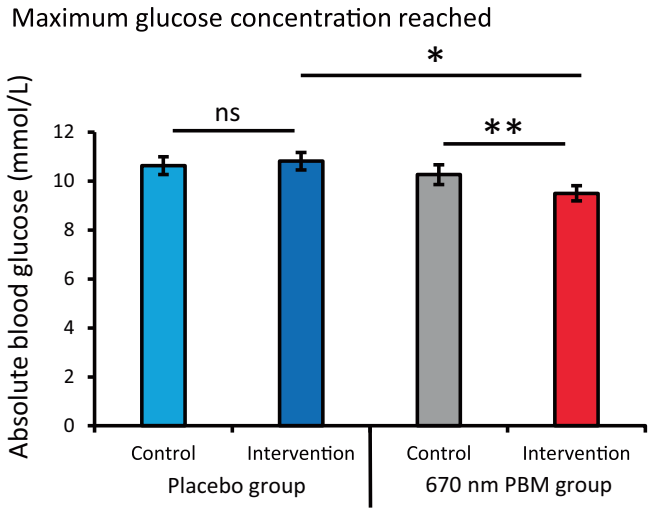


FIGURE 4 Effect of 670 nm photobiomodulation (PBM) on blood glucose concentration spikes. Maximum blood glucose concentrations reached were significantly reduced when comparing 670 nm PBM intervention against the placebo intervention. A significant reduction in the maximum blood glucose concentration reached was observed following 670 nm PBM (red bar) when compared with a control result from the same participants (grey bar). There was no difference observed between the maximum oral glucose tolerance test result following placebo intervention when compared with its preceding control from the same participant group (blue bars). *$p < 0.05$, **$p < 0.01$, ns, not significant. Error bars are standard error of the mean.

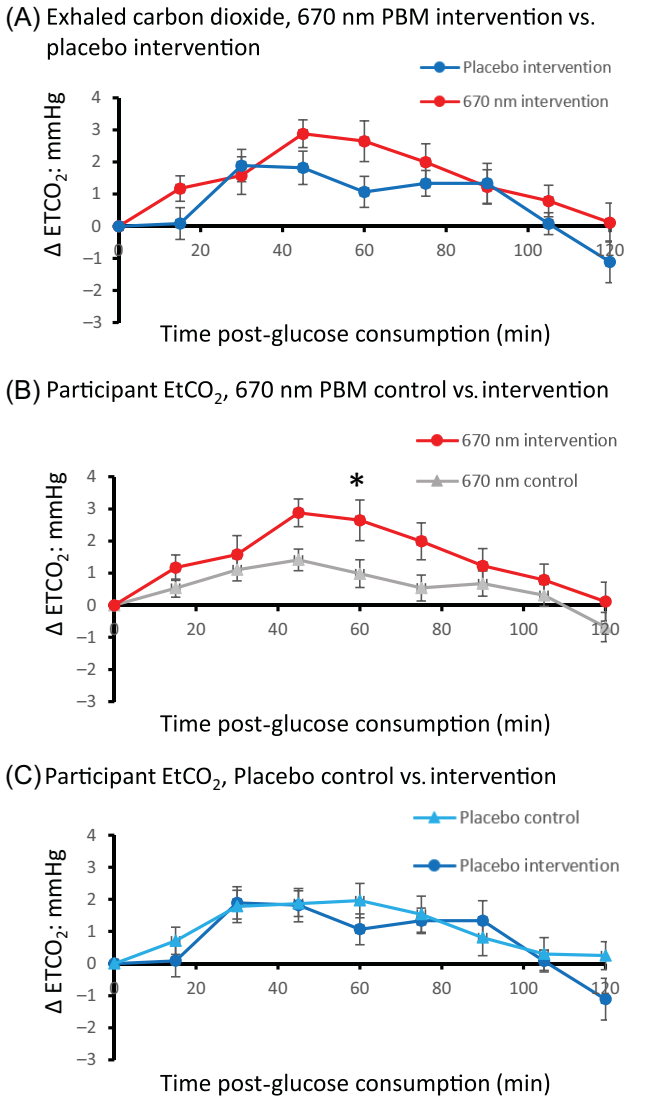


FIGURE 5 A 670 nm photobiomodulation (PBM) increases exhaled carbon dioxide partial pressure. End-tidal CO_2 ($EtCO_2$) was recorded by side stream capnometry, every 15 min for 2 h, following a fasted oral glucose tolerance test. The expected increase in exhaled CO_2 partial pressure following glucose ingestion was observed across both groups for each visit (A–C). No statistically significant difference was found between the 670 nm PBM and Placebo intervention groups ($p = 0.21$) (A). Within the 670 nm PBM group, exposure to 15 min of 670 nm light, was found to induce a significant increase in $EtCO_2$ (multivariate analysis of variance, $p = 0.03$) compared with the control data (visit 1) from each participant (B). Post hoc analysis indicates a statistically significant increase in $EtCO_2$ at 60 min, when compared against 670 nm PBM control visit data (B). No statistically significant difference was observed between the control and intervention results from the placebo group (C). *$p < 0.05$. Error bars are standard error of the mean.

point 0 min reports deviation of blood glucose concentration following glucose consumption. When comparing the effect of a 670 nm PBM intervention against placebo in area under the curve, PBM reduced overall blood glucose concentrations by 7.3% (Figure 2C, $p = 0.0061$). In data from analysis baselined against their initial glucose measurement, the post-consumption elevation in blood glucose was reduced by 27.7% (Figure 2D, $p = 0.0002$).

A repeated measures ANOVA confirmed a significant difference in absolute blood glucose concentration ($p = 0.035$) and in the post-consumption elevation in glucose concentration from baselined data ($p = 0.049$). Post hoc analysis highlighted significant decreases in both measures at time points of 45-, 60-, 75-, and 90-min post-loading (Figure 2A,B).

There are variations in the OGTT response between individuals [20, 24] that may influence the observations seen between groups. To confirm any findings, paired participant analyses were performed, comparing individuals' responses without intervention (control) against their subsequent results post-670 nm PBM (Figure 3A–H). Within the 670 nm PBM group, PBM reduced the absolute blood glucose concentration (Figure 3A), $p = 0.08$ MANOVA, with a Wilks' lambda $F = 40.5$, $p < 0.001$, indicating possible significance at individual timepoints. Discreet timepoint significant differences were confirmed with post hoc analysis. When these data are re-baselined to timepoint 0 there is a

similar reduction in blood glucose (Figure 3B, $p < 0.001$). In both methods of comparison (Figure 3A,B) post hoc analysis shows significant difference in concentration 60-min post-glucose consumption, with the significant difference maintained before returning to normal at 2 h.

Absolute glucose concentration throughout the OGTT was assessed using area under the curve analysis, which showed a 7.9% reduction in absolute blood glucose concentration during the OGTT following PBM (Figure 3C, $p = 0.0012$). Baselined Data for changes in blood glucose after resorption was reduced by 26.3% following 670 nm PBM (Figure 3D, $p = 0.0008$).

Within-participant data for the placebo group, comparing placebo control and placebo intervention results, showed no difference in blood glucose concentration between the control visit and intervention visits (Figure 3E–H).

This study also investigated the effect of 670 nm PBM on blood glucose spiking. Comparing 670 nm PBM and placebo interventions revealed a reduction of 12.1% in the peak glucose concentration reached, down from 10.8 to 9.5 mmol/L ($p = 0.0102$; Figure 4). Separately, paired analysis within the 670 nm group gave a 7.5% reduction in maximum glucose peak level, down from 10.3 to 9.5 mmol/L ($p = 0.0054$), with no significant differences in maximum glucose level reached in the paired placebo group analysis (Figure 4). These changes were obtained with only 15 min of exposure over 800 cm^2 tissue area, accounting for ~4% of the skin surface area [25].

3.2 | Effect of red light on exhaled carbon dioxide

Reduced blood glucose may result from increased glucose oxidation, or from increased glucose storage as glycogen. Increased oxidation would lead to elevated CO_2 production and may be detectable in exhaled breath. Here, $EtCO_2$ increased during all glucose tolerance tests (Figure 5A–C) [26]. No significant differences were observed between 670 nm PBM intervention and placebo intervention (Figure 5A). However, a significant difference in $EtCO_2$ was observed between the 670 nm PBM intervention and their paired participant control visit results across the OGTT time course (MANOVA, $p = 0.03$; Figure 5B). No significant difference in breath rate was observed for any intervention.

4 | DISCUSSION

This study has shown that a single 15-min exposure to 670 nm significantly reduces blood glucose using a standard oral glucose tolerance test. It also has limited impact on expired CO_2 consistent with elevated respiration. While glucose is a vital nutrient, sustained high levels in the blood induce inflammation and insulin resistance in vascular endothelial cells [27]. A reduction in circulating concentration of glucose after eating (post-prandial) is beneficial in those with impaired blood glucose homeostasis. However, the degree of post-prandial hyperglycaemia and other fluctuation in blood glucose levels may contribute to the pathogenesis of diabetic complications [28]. Fluctuations are more damaging than sustained hyperglycaemia, as an intermittent high glucose exposure further increases endothelial cell apoptosis rate [29]. Hence, clinical intervention routinely includes practices to minimise sharp fluctuations in blood glucose levels [30]. We report that 670 nm PBM decreases maximum glucose levels reached post-glucose consumption, and therefore offers an intervention to limit glucose spiking. However, it is important to stress that this study has been undertaken using normal healthy subjects, not those that are diabetic. A bridge between our data and diabetic subjects has yet to be made.

A 670 nm PBM has been demonstrated to improve mitochondrial membrane potential and increase ATP production via elevated oxidative phosphorylation. This has been shown to translate into improved CNS function. This is preserved across species from fly to human [1, 2, 4, 8, 12, 31, 32]. A 670 nm PBM impact is marked in tissues with high metabolic demand and in those that have declined through age or disease. Its widespread positive influence likely rests on the large energy demand made by membrane pumps particularly in the CNS.

Increases in ATP following 670 nm PBM in mice range from ~20% in the retina to >50% in the brain [5]. In whole flies, it is ~30% [13]. Because increased ATP production needs to be fuelled by glucose and oxygen, we established the hypothesis that 670 nm PBM may have the ability to reduce blood glucose. The data presented here are consistent with this hypothesis.

In this study participants were exposed to 670 nm PBM 45 min prior to glucose consumption, and circulating blood glucose concentrations were significantly reduced 45-min post-consumption, revealing that onset of the effect is ~1.5 h. This reduction was observed following only local light exposure. However, 670 nm PBM has been shown to have an abscopal effect [17, 33]. Shifting local mitochondrial function has been shown to result in mitochondrial changes in other distal organs [34]. The potential signalling route by which this may occur has recently been revealed, as mice exposed to 670 nm PBM have widespread and significant changes in large numbers of circulating cytokines that have the ability to act as signalling molecules [14]. Alternatively, it has been argued that blood contains cell-free, respiratory

competent mitochondria [35, 36]. These could also play a role in the systemic impact of local 670 nm PBM.

It remains to be explored if using 670 nm could impact on diabetes and our results cast no light upon this question. But it is clear that light impacts on mitochondrial function. Longer wavelengths, particularly 670 nm have consistently been shown to improve their function in a manner that can be translated into improved overall physiology and performance [1, 10, 12, 17, 37], whereas shorter wavelengths undermine mitochondrial function [38–40]. Exposure to 450 nm, which is a dominant peak in LED lighting in the built environment, results in significant and rapid reduction in blood pressure in humans and also a significant increase in heart rate. Both shifts persist during exposure periods [41]. Experiments using 468 nm PBM in human subjects similarly disrupted physiology significantly increasing blood glucose levels during exposure [42]. LED lighting is fundamentally blue dominant as short wavelength light is used to stimulate a phosphor element that then is perceived by the human eye to produce a wider spectral range of white light. However, LEDs fundamentally lack longer wavelengths. They peak strongly around 450 nm, but have little content beyond 620 nm [43–45]. Hence, lengthy exposure to them in the absence of sunlight may have significant long-term consequences for human health including dysregulation of blood sugars. This problem remains to be fully appreciated but is likely to be a potential public health issue.

AUTHOR CONTRIBUTIONS

Michael B. Powner and Glen Jeffery: Project conception; study design; data collection; data analysis and interpretation; wrote the article.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available through FigShare; 10.6084/m9.figshare.24773346.

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