Optical stimulation of mitochondria reduces blood glucose levels

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Article

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Abstract

Mitochondria regulate metabolism, but solar light influences its rate. Red light increases mitochondrial membrane potentials and ATP production and may increase glucose demand. Here we show, with a glucose tolerance test, that red light exposure in 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%, over 2 h. Maximum glucose spiking was reduced by 5.1%. Decreased blood glucose correlated with increased exhaled end-tidal CO$_2$ partial pressure at 1 h, indicating the mechanism includes an increased oxidation rate. Consequently, 670 nm light exposure can be used to reduce blood glucose spikes following meals. This may reduce damaging fluctuations of blood glucose on the body, a major risk factor for diabetic complications, offering a safe, non-invasive intervention for glucose management of diabetes at home.

Introduction

Red light (~ 650–800 nm) stimulates mitochondrial respiration, shifting their metabolism. This photobiomodulation, alters cellular respiration rate, increases membrane potential, ATP production and subsequently reduces reactive oxygen species and inflammatory markers. [1, 2, 3] This results in improved sensory and motor function, including aged human colour perception. [4, 5, 6] 670 nm and other, longer wavelengths of red/near infra-red light are absorbed by the nanoscopic interfacial water layer surrounding mitochondrial ATP rotor pumps. [7] The energy transfer reduces water viscosity, allowing the rotor pump to achieve greater momentum, and increases ATP production. [7] An increase in ATP production rate requires more fuel. Glucose is the primary fuel source in animals and, as shown previously, systemic glucose concentrations decrease in an invertebrate model (bees) following a single 670 nm light exposure. [8] This result potentially has significance for human health, particularly in diabetes management and weight control. Here we have extended these findings from invertebrates into humans, demonstrating that a non-pharmaceutical, non-invasive, optical intervention can be used to support blood glucose level management.

Results

Participants were randomised into either a 670 nm group (n = 15), or placebo (no light) group (n = 15). All individuals undertook fasting oral glucose tolerance tests (OGTT), consuming 75g 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$_2$) was measured every 15 min for 2 h while at rest. For all individuals in both groups an initial baseline (control) OGTT was recorded.

Within 7 days, a second OGTT was administered during which the 670 nm group received a 15 min light exposure of 40mW cm$^{-2}$ (28,800 J) across an area of 800 cm$^2$ of skin of the upper back starting 45 min prior to consuming glucose, with the light not turned on for the placebo group. Energies and timings of lights are consistent with previous studies. [9] Three comparisons were made between OGTTs for
analysis. (1) The 670 nm and placebo intervention results were compared across the two subject populations. To ensure any results found were not caused by marked individual variabilities, paired within-participant comparisons were made between (2) the no 670 nm control against 670 nm exposure results and (3) no placebo control against placebo intervention results.

**Effect of red light on blood glucose parameters**

Following glucose loading in the OGTT, initial blood glucose levels over the first 30 min were similar in both 670 nm exposed and placebo interventions (Fig. 1a). Blood glucose levels were always elevated above fasting levels following glucose consumption (Fig. 1). When comparing 670 nm against placebo interventions, 670 nm light reduced this elevation in blood glucose by 27.7% over the 2 h OGTT, as determined by area under the curve ($p = 0.0002$) (Fig. 1a). A repeated measures ANOVA confirmed a significant difference ($p = 0.049$) with post hoc analysis highlighting significant decreases found at specific time points of 45-, 60- and 90-min post-loading (Fig. 1a). These relative decreases resulted in the absolute blood glucose level, not baselined to change from fasting level, being reduced by 7.3% ($p = 0.0061$) between 670 nm and placebo interventions. The magnitude of this response following exposure of only a limited area of tissue, is likely the result of wider indirect metabolic upregulation, [10] potentially via distal mitochondrial communication. [11]

Paired participant analyses confirmed this result. Within the 670 nm group, the elevation of blood glucose after loading was reduced by 26.3% ($p = 0.0008$) following 670 nm exposure, with a significant effect found at 60 min post-loading and return to baseline at the final blood collection after 120 min (Fig. 1b). Absolute blood glucose levels compared, without baselining to fasting levels, were decreased by 7.9% ($p = 0.0012$). Within-participant data for the placebo group, comparing control visit and placebo intervention, showed no difference in blood glucose levels (Fig. 1c).

Here, we have also looked into the effect of 670 nm light on blood glucose spiking; maximum glucose levels reached, recorded in mmol/L, were reduced following 670 nm light exposure. Comparing 670 nm and placebo interventions revealed a reduction of 5.1% in the peak glucose concentration reached, down from 10.8 mmol/L to 10.2 mmol/L ($p = 0.0102$) (Fig. 1d). Separately, paired analysis within the 670 nm group gave a 7.5% reduction in maximum glucose peak level, down from 10.3 mmol/L to 9.5 mmol/L ($p = 0.0054$), with no significant differences in maximum glucose level reached in the paired placebo group analysis (Fig. 1d). These changes were obtained with only 15 minutes of exposure time over 800 cm$^2$ tissue area, accounting for approximately 4% of the skin surface area. [12]

**Effect of red light on exhaled carbon dioxide**

Reduced blood glucose levels may result from an increased glucose oxidation rate, or through an increased storage of the ingested glucose as glycogen. Increased oxidation would lead to increased CO$_2$ production and would be detectable through exhaled breath. Here, EtCO$_2$ increased during all the glucose tolerance test (Fig. 2a-c), while participants were at rest, consistent with elevated carbohydrate intake. [13]
No significant differences were observed between 670 nm and placebo groups (Fig. 1a). However, a significant difference in EtCO$_2$ was observed 60 min post glucose loading when comparing 670 nm exposed participants against their no intervention control results (Fig. 2b). This correlates with the first time point of significant reductions in blood glucose level (Fig. 1b). No significant difference in breath rate was observed for any intervention. The observed change in CO$_2$ production is consistent with increased oxidation of glucose as a mechanism, supported by previous invertebrate experiments, where 670 nm exposure increased resired CO$_2$ volume [14] [see their Fig. 1A], while not ruling out contribution from increased glucose storage.

**Discussion**

This study has shown that a single 15 min exposure to 670 nm light significantly reduces the amount of glucose loaded into the blood during a standard oral glucose tolerance test. While glucose is a vital nutrient, sustained high levels in the blood induce inflammation and insulin resistance in vascular endothelial cells. [15] A reduction in glucose loading 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. [16] Fluctuations are more damaging than sustained hyperglycaemia, as an intermittent high glucose exposure further increases endothelial cell apoptosis rate. [17] Hence, clinical intervention routinely includes practices to minimise sharp fluctuations in blood glucose levels in diabetic patients. [18] We report that 670 nm exposure decreases maximum glucose levels reached post glucose challenge, and therefore offers an intervention to limit glucose spiking.

The effect of red light exposure is consistent across species, [19, 20, 21] however the timing of onset has not been fully explored. Here, participants were exposed to red light 45 min prior to glucose loading, and blood glucose levels were significantly reduced 45 min post loading (Fig. 1a), revealing that onset of the effect is within ~ 1.5 h. This is within the time frame of improved retinal function following red light exposure in aged human subjects. [6] Significant reduction in blood glucose was observed following local red light illumination of the body, rather than requiring whole body exposure. Red light exposure has been shown to have an abscopal effect [22] and results in systemic changes in cytokine expression in the blood [23]. It is likely that this systemic cytokine change may play a role in the marked widespread changes in blood glucose to a distal region of illumination. Alternatively, blood contains cell-free, respiratory competent, mitochondria [24, 25] which may also be modulated by the red light and signal changes systemically as they circulate.

670 nm light increases ATP levels, [1] via increasing mitochondrial oxidative phosphorylation. [2, 7] An increased facilitated diffusion rate of glucose into cells to meet increased intra-cellular demand by 670 nm absorption, is the likely mechanism that results in reduced blood glucose. Increased EtCO$_2$ levels observed in paired participant analysis of the 670 exposure group (Fig. 2b), whilst the participants were at rest, could result from increased oxidation. However, stimulation of glucose incorporation into carbohydrate stores cannot be excluded as an alternative mechanism involved.
Diabetes mellitus encompasses a group of etiologically different metabolic diseases and is characterised by impaired or loss of glucose homeostasis, leading to high blood glucose levels. It is the most common metabolic disorder worldwide and a major risk factor for cardiovascular disease. Type I diabetes results in elevated blood glucose levels due to reduced insulin secretion from a loss of pancreatic β-cells. While, the predominant form, Type II diabetes is typified by insulin insensitivity leading to a loss of insulin activation of cells in peripheral organs (particularly liver and skeletal muscle), resulting in reduced glucose uptake. [26] Concurrently, in Type II diabetes, pancreatic insulin secretion may be reduced and so is insufficient to meet the higher demand. [27] Glucose intolerance resulting in significantly elevated post-prandial blood glucose levels and elevated fasting glucose levels (5.6-7.0 mmol/L; American Diabetes Association, 6.1-7.0 mmol/L; World Health Organisation) often precedes Type II diabetes and is referred to as pre-diabetes. [28] People who are pre-diabetic are at five to six fold greater risk of developing Type II diabetes. Each of these three impaired metabolic states (Type I and Type II diabetes, and pre-diabetes) may benefit from photobiomodulation with 670 nm light to reduce post prandial blood glucose fluctuations that increase the risk of diabetic complications, such as nephropathy, retinopathy, or cardiovascular disease. [29]

Mitochondrial oxidation rate peaks in the morning, coincident with the known surge of blood glucose. [30] Morning is the only time widow when 670 nm exposure is effective at manipulating mitochondrial function. [6, 30] Hence, a brief exposure as a part of an early daily routine could be incorporated into normal life, supporting current recommended glucose control measures.

**Methods**

**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 group (mean age 41.1 ± 13.1 years), 15 in the placebo group (no light) (mean age 38.3 ± 13.7 years), with no known metabolic conditions and not taking medication known to effect metabolism.

**Oral glucose tolerance test and Blood glucose monitoring**

Participants fasted overnight, consuming only water for at least 10 hours prior to the oral glucose tolerance test (OGTT). An initial finger prick capillary blood glucose levels was measured using a blood glucose monitor (Kinetik Wellbeing, UK), a method with proven sensitivity vs venous glucose levels, for use in OGTT. [31] Forty-five minutes later an OGTT was performed. Participants consumed 75g glucose in water (total volume of 150ml), within 2 minutes. Following glucose consumption, further finger prick blood glucose concentrations were measured at 0 (fasted), 15, 30, 45, 60, 75, 90, 105, 120 min after administration of glucose solution.
Respiratory measurements

End-tidal partial pressure of carbon dioxide (EtCO$_2$) in expired gas, and breath rate were measured at the same time intervals as blood glucose (-45, 0, 15, 30, 45, 60, 75, 90, 105, 120 min after administration of glucose solution) via capnometry, using a PC-900B Hand Held SideStream EtCO2 monitor (PROACT medical, UK), and nasal cannula.

Light exposure

All participants undertook an OGTT on two separate occasions. During the first visit, they underwent an OGTT with a full set of glucose and respiration measurements without intervention (baseline measurements, control). Participants were randomised into the intervention group or the placebo group at the point of recruitment; during their second visit there was an intervention step added to the protocol. In the 670 nm group, immediately following initial blood glucose levels being recorded (-45 min), participants exposed a 800 cm$^2$ region of upper back to 670 nm light for 15 min at an intensity of 40mW cm$^{-2}$ (28,800 J). With a penetration depth of approximately 2 mm that would include the cells of the skin and underlying musculature [32] (including the trapezius). Light was delivered via LEDs; 670 nm was the peak wavelength, with a half power band of approximately 10 nm. 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 which group they were randomised into. The placebo group underwent the same procedure, except the LED array was not switched on during their intervention OGTT.

Statistical analysis

The initial measurement at 0 min was used in analysis of change from fasting levels due to the variation in initial blood glucose concentration and EtCO$_2$ partial pressures between participants. Glucose loading in the blood over the 2 h OGTT was determined by measuring the area under the curve. This was carried out assuming linear lines between data points at sequential time intervals. For inter group comparisons (670 nm 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 (ANOVA) using a general linear model with repeat measures, with post hoc Mann Whitney U test was used to test for significant difference between 670 nm and placebo interventions, while 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.

Declarations

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Author contributions
MBP and GJ; project conception, study design, data collection, data analysis and interpretation, wrote the manuscript.

Data availability statement

The data that support the findings of this study are available through FigShare;


References

8. Powner, M. B., & Jeffery, G. Systemic glucose levels are modulated by specific wavelengths in the solar light spectrum that shift mitochondrial metabolism. Plos one 17(11), e0276937 (2022).


Figures
Exposure to 670 nm light reduces blood glucose levels. (a) Capillary blood glucose concentrations were taken every 15 min for 2 h, following a fasted oral glucose tolerance test (OGTT). Exposure to 15 min of 670 nm light (28,800 J) (n= 15), starting 45 min prior to OGTT, significantly reduced blood glucose levels, from time point +45 min, compared to a placebo intervention (no light, n= 15). Area under the curve analysis shows a 27.7% reduction in mean glucose loading post glucose consumption (p= 0.0002), while
a repeated measures ANOVA confirms a significant difference between the two groups \((p = 0.049)\). Post hoc analysis conformed which specific time points showed differences (b) Glucose response within a single population, with and without 670 nm exposure; initially no 670 nm was given, and an OGTT carried out, subsequently they were re-tested and exposed to 670 nm. 670 nm in these individuals significantly reduced blood glucose loading of the blood. Area under the curve analysis showed a 26.3\% reduction \((p = 0.0008)\) and this was confirmed by repeated measures ANOVA \((p<0.001)\). Reduced elevation was time dependent and observed after time point +60 min of the OGTT. (c) Glucose response within a single population was carried out as above for the placebo intervention; there were no significant differences found. (d) Maximum glucose levels reached were significantly reduced between 670 nm and placebo interventions. There was a significant reduction in maximum glucose level reached with 670 nm exposure, compared to the preceding control with no light exposure. There was no difference observed between the maximum OGTT result following placebo interventions compared to its preceding control. *; \(p<0.05\), **; \(p<0.01\), ***; \(p<0.005\), ns; not significant. Error bars are standard error of the mean. Statistical analysis: ANOVA using a general linear model with repeat measures, with post hoc Mann Whitney U test was used for between group analysis, and Wilcoxon Signed Rank Test for single participant (paired) analysis (all two tailed tests).
670 nm light 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 all four groups (a-c). No statistically significant difference was found between the 670 nm and Placebo intervention groups ($p=0.21$) (a). Within the 670 nm group, exposure to 15 min of 670 nm light (28,800 J) (n= 15), was found to induce a significant increase in EtCO$_2$ (ANOVA, $p=0.03$) (b). With post hoc analysis highlighted a statistically significant increase in EtCO$_2$ at 60 min, when compared against paired
participant data recorded with no 670 nm light (b). *; p< 0.05. Error bars are standard error of the mean.
Statistical analysis: ANOVA using a general linear model with repeat measures, with post hoc Mann Whitney U test was used for between group analysis, and Wilcoxon Signed Rank Test for single participant (paired) analysis (two tailed tests).