Brain, nutrition and metabolism

Studies in lean, obese and insulin resistant humans

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Acute effects of morning light on plasma glucose and triglycerides in healthy men and men with type 2 diabetes

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Abstract

Ambient light intensity is signalled directly to hypothalamic areas that regulate energy metabolism. Observational studies have shown associations between ambient light intensity and plasma glucose and lipid levels, but human data on the acute metabolic effects of light are scarce. Since light is the main signal indicating the onset of the diurnal phase of physical activity and food intake in humans, we hypothesized that bright light would directly affect glucose and lipid metabolism. Therefore we determined the acute effects of bright light on plasma glucose and lipid concentrations in two randomized cross-over trials: 1) in 8 healthy lean men and 2) in 8 obese men with type 2 diabetes. From 07:30, subjects were exposed to either bright light (4000 lux) or dim light (10 lux) for 5 hours. After one hour of light exposure, subjects consumed a 600 kcal mixed meal. Primary endpoints were fasting and postprandial plasma glucose levels. In healthy men, bright light did not affect fasting or postprandial plasma glucose levels. However, bright light increased fasting and postprandial plasma triglycerides. In men with type 2 diabetes, bright light increased fasting and postprandial glucose levels. In men with type 2 diabetes, bright light did not affect fasting triglyceride levels but increased postprandial triglyceride levels. We show that ambient light intensity acutely affects human plasma glucose and triglyceride levels. Our findings warrant further research into the consequences of the metabolic effects of light for the diagnosis and prevention of hyperglycemia and dyslipidemia.
Introduction

In modern societies, people are increasingly exposed to artificial light (1). Intrinsically photosensitive retinal ganglion cells detect ambient light intensity and relay this information directly to hypothalamic areas, including the central brain clock in the suprachiasmatic nucleus (SCN) (2). The SCN has a role in appetite control, presumably via its connections to the arcuate nucleus and the lateral hypothalamus. In addition, the SCN controls glucose metabolism via autonomic and hormonal pathways (3). Therefore, ambient light may affect food intake and glucose metabolism (4).

In mice, chronic exposure to dim light at night (5) or continuous light (6) induces obesity and hyperglycemia, and also exposure to prolonged day-length induces obesity (7). In rats, a single light pulse acutely increases expression of the gene encoding the gluconeogenic protein phosphoenolpyruvate carboxykinase (PEPCK) in the liver, via activation of the autonomic nervous system (8). Observational human studies also suggest adverse metabolic effects of ambient light at night. Exposure to light at night is associated with obesity (9, 10), increased fasting triglycerides (10) and diabetes (11, 12). Furthermore, shift workers are at increased risk to develop obesity and type 2 diabetes (12).

In comparison with the observations on chronic light at night (i.e. light at the inappropriate circadian phase), there are less human studies on the metabolic associations of light during the day (i.e. light at the appropriate circadian phase). One study describes a positive association between daytime light exposure and BMI (13). Two studies show that several weeks of morning light therapy may cause a slight reduction in fat mass (despite no effect on body weight) in obese subjects (14, 15). There is a case report describing a patient with seasonal affective disorder (SAD) and insulin dependent diabetes who showed a strong reduction of insulin requirements after three weeks of morning light therapy (16), and another case report describes a similar patient who showed increased insulin sensitivity after ten morning sessions of thirty minutes 10.000 lux light therapy (17).

Despite these chronic studies, human data on the acute metabolic effects of light are scarce. One recent study investigated the effects of blue enriched light in the morning or the evening and showed increased insulin resistance due to blue enriched bright (260 lux) light exposure compared to dim (<20 lux) light in the morning and the evening (18). Since daylight is the main signal indicating the onset of the active circadian phase (i.e. the phase of physical activity and food intake) in humans, we hypothesized that bright light with the intensity of daylight would directly affect glucose and lipid metabolism. Therefore, we determined in healthy men the acute effects of bright light (4000 lux, the intensity of outside light intensity on a cloudy day (19)) on fasting and postprandial plasma glucose and lipid levels, compared to dim light (10 lux, the intensity of candle-light (19)). Subsequently, since patients with type 2 diabetes per defition have increased fasting and postprandial glucose levels compared to healthy subjects (20), we investigated the effects of bright light on fasting and postprandial plasma glucose and lipid levels in men with type 2 diabetes.
Materials and methods

Subjects and setting

We performed two clinical trials. In the healthy subject trial we included 8 healthy lean men (inclusion criteria: age 18-50 years, BMI 18-25 kg/m², fasting plasma glucose <5.6 mmol/l, habitual wake-up time 6:00-9:00). In the type 2 diabetes patient trial we included 8 obese men with type 2 diabetes (inclusion criteria: age 18-80 years, BMI >25 kg/m², fasting plasma glucose >6.9 mmol/l or HbA1c >6.5% (48 mmol/mol), habitual wake-up time 6:00-9:00). The trials were not designed to make a direct comparison between the two subject groups. We included only men, since the reported effects of the menstrual cycle on insulin sensitivity (21, 22) predict larger inter-individual variation in women, and therefore a larger sample-size would be needed to obtain sufficient power for a similar study in women.

Exclusion criteria for both trials were the use of any medication (other than metformin for the men with type 2 diabetes) interfering with glucose metabolism or neuronal functioning, any gastro-intestinal or metabolic disease affecting digestion or metabolism (mild gastroesophageal reflux disease was allowed), neuropsychiatric illness, epilepsy, uncontrolled hypertension, ophthalmological abnormalities including diabetic retinopathy, and (because of the composition of the experimental meals) lactose intolerance or soy allergy. Subjects were recruited via local advertisements.

The healthy subject trial was registered at the Netherlands Trial Registry (NTR) as NTR3881. The type 2 diabetes patient trial was registered as NTR4645. Both trials were approved by the Institutional Review Board of the Academic Medical Center, and conducted according to the Declaration of Helsinki of October 2008.

Study design

Both trials were performed using the same study protocol, with additional measurements in the type 2 diabetes patients. The design was a 2-week randomized cross-over intervention trial. At baseline, subjects underwent a physical exam and provided a fasting blood sample. Subsequently, participants were admitted to the clinical research unit twice, with a one week interval. Subjects were randomized to start with either bright light or dim light using a randomization list generated with nQuery Advisor 7.0 (Statistical Solutions Ltd, Cork, Ireland).

Prior to each admission, subjects were asked to maintain their normal sleep-wake schedule for 5 days, to refrain from excessive exercise for 1 day and to use at most 3 alcoholic beverages per day for 3 days. To verify sleep-wake behavior, subjects completed a 5-day sleep-wake diary. Patients with type 2 diabetes discontinued metformin use three days prior to each admission.

Subjects entered the clinical research unit after a one hour fast at 20:00 (Fig. 1). At 21:30 subjects received a standard 800 kcal mixed meal consisting of 300 ml tomato soup and 179 g baguette with margarine and cheese (Albert Heijn, the Netherlands). Subjects remained in normal room light (200 lux) until
23:30 and slept in darkness until 07:30. In the dim light condition, subjects were subsequently exposed to 10 lux emitted by one HF3319 EnergyLight (Philips, Eindhoven, the Netherlands) placed in the room corner. In the bright light condition, subjects were instead exposed to 4000 lux bright light emitted by two HF3319 EnergyLights (Philips) placed in front of the subject. Ten lux is comparable to the light intensity of candle-light and 4000 lux is comparable to outside light intensity on a cloudy day (19). All light intensities were verified at the participant’s eye level with a LM-120 Lightmeter (Amprobe, Everett, WA, USA). A cannula was inserted in a peripheral arm vein at 8:00. At 08:30 participants consumed a 600 kcal liquid mixed meal within 5 min, consisting of 400 ml Ensure Plus Vanilla (carbohydrates 54 energy%, fat 29 energy%, protein 17 energy%, Abbott Nutrition, Columbus, Ohio, USA). Blood samples were obtained before the meal at 8:15 and 8:25 and postprandially at 8:35, 8:40, 8:45, 8:50, 9:00, 9:15, 9:30, 9:40, 9:50, 10:00, 10:30, 11:00, 11:30, 12:00, 12:30 and 13:30. The frequency of blood sampling was increased at postprandial times with predicted rapid changes in glucose or insulin levels (based on (23, 24)) to facilitate minimal model analyses. Heart rate was continuously monitored with a holter ECG device (GE Healthcare, UK) connected to the chest. During admission, subjects remained in a semi-recumbent position and they were not allowed to use electronic devices such as smart-phones or laptops to prevent unwanted light exposure.

The experimental design of the type 2 diabetes patient trial was identical to the healthy subject trial with the addition of the following measurements. Saliva samples were obtained at regular intervals. Hunger, prospective food consumption, fullness and satiety were assessed using a validated questionnaire (25).

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**Figure 1. Study design.** The healthy subject trial and the type 2 diabetes patient trial were both designed as a randomized cross-over intervention trial. Subjects were admitted to the clinical research unit twice, with a one week interval. Subjects entered the clinical research unit after a one hour fast at 20:00. At 21:30 subjects received a standard 800 kcal mixed meal, and they were allowed to sleep in darkness from 23:30 until 07:30. In the dim light condition, subjects were subsequently exposed to 10 lux emitted by one HF3319 EnergyLight (Philips) placed in the room corner. In the bright light condition, subjects were instead exposed to 4000 lux bright light emitted by two HF3319 EnergyLights (Philips) placed in front of the subject. A cannula was inserted in a peripheral arm vein at 8:00 and frequent blood samples were obtained from 8:15. At 08:30 participants consumed a 600 kcal liquid mixed meal. In the type 2 diabetes patient trial, additional measurements were performed: saliva samples (asterisk) were obtained at regular intervals, and hunger, prospective food consumption, fullness, and satiety were assessed with a questionnaire.
Endpoints and sample size determination

For both trials, the primary endpoints were fasting and postprandial plasma glucose levels. Secondary endpoints were fasting and postprandial plasma levels of insulin, free fatty acids and triglycerides, and fasting and postprandial heart rate variability. For fasting plasma glucose values, both studies were powered to detect a difference of 0.5 mmol/L with a power of 80%, a significance level of 0.05 and an estimated standard deviation of differences of 0.5 mmol/L. For postprandial glucose values, both studies were powered to detect a difference of 100 mmol·min⁻¹/L in the incremental area under the curve (iAUC) or area under the curve (AUC) of postprandial glucose excursions, with a power of 80% and a P value of 0.05 and a standard deviation of 110 mmol·min⁻¹/L. Power analysis was performed using nQuery Advisor 7.0.

Measurements

Blood samples were centrifuged for 10 minutes at 3000 rpm at 4°C and plasma was separated from the cells. Glucose was determined immediately using the glucose oxidation method with the Biosen glucose analyzer (EKF Diagnostics, Barleben, Germany). Plasma aliquots were temporarily stored at -20°C. HbA1c, plasma insulin and plasma triglyceride levels were measured as described previously (26), C-peptide was determined with a ¹²⁵I radioimmunoassay (Linco Research, Inc, USA), and plasma free fatty acid (FFA) levels were determined with an enzymatic calorimetric method (NEFA-HR(2) test kit, Wako Chemical, Neuss, Germany). In patients with type 2 diabetes, two additional measurements were performed: plasma glucagon was determined with a ¹²⁵I radioimmunoassay (Millipore, Billerica, MA, USA) and saliva cortisol was determined by on-line solid phase extraction LC/MS/MS (Waters Corporation, Milford, MA, USA).

Heart rate variability

We analysed holter ECG recordings with automated QRS detection followed by manual correction of noise and missed beats using a MATLAB (v 2013b, The MathWorks Inc., Natick, MA, USA) based application, as described previously (27). Subsequently we performed heart rate variability (HRV) analysis on one-hour bins using the Kubios HRV software (version 2.2, University of Eastern Finland) (28). As an indication of sympathetic/parasympathetic balance, we calculated the low frequency (LF)/high frequency (HF) ratio with the frequency domain method.

Beta cell function and insulin sensitivity

To assess pancreatic beta cell function and peripheral insulin sensitivity, plasma glucose, insulin and C-peptide levels were used to fit model parameters in the oral C-peptide minimal model and the oral glucose minimal model. The C-peptide minimal model is a two compartment model that predicts C-peptide concentrations in response to a static glucose-dependent term and a dynamic glucose-dependent term. The C-peptide minimal model outputs are the static time constant $k_g$ that represents the amount of secreted C-peptide per minute.
for a certain plasma glucose level above the static glucose threshold $h$ and the dynamic constant $k_d$ that represents the amount of secreted C-peptide induced by the change in plasma glucose (29-31). The oral glucose minimal model is based on the intravenous glucose minimal model (32) and consists of two ordinary coupled differential equations, predicting plasma glucose concentration based on the observed insulin concentration. The insulin sensitivity index $S_I$ is derived from the model parameters (33). Fitting was performed with the MATLAB\textsuperscript® GlobalSearch algorithm. Details on the models and parameter fitting are presented in the online supplemental materials.

**Statistical analysis**

Normally distributed variables are presented as mean ± standard deviation (for baseline measurements) or mean ± standard error of the mean (for outcome data), and non-normally distributed variables as median (25\textsuperscript{th} percentile-75\textsuperscript{th} percentile).

Fasting plasma values were defined as the average of 8:15 and 8:25 values. For postprandial plasma values, AUC and iAUC values were calculated using GraphPad Prism for Windows (version 5.01; GraphPad Software, Inc.). Since FFA levels are suppressed after the meal, for FFA the area above the curve was calculated. The effects of light on fasting plasma levels, postprandial AUC, iAUC, area above the curve and appetite scores were determined with a two-sided paired samples Student’s T-test for normally distributed variables and with a Related-Samples Wilcoxon Signed Rank test for non-normally distributed variables.

HRV data were analyzed in a single analysis with all time points after lights on using a generalized linear mixed model with Time (nominal), Light and their Interaction as fixed effects. If a significant Interaction or Light effect was present, post hoc tests were performed with a Related-Samples Wilcoxon Signed Rank test. A random intercept and slope were fitted where appropriate and robust covariances were used to test the fixed effects. If no significant Interaction was detected, the model was repeated with only the fixed factors Time and Light. All statistical analyses were performed using P=0.05 as significance level with IBM SPSS Statistics (version 21; SPSS, Chicago, IL, USA).
Results

Healthy men

Participants
For the healthy subject trial, 14 subjects were screened and 8 subjects were included (2 subjects did not meet inclusion criteria, 4 subjects declined participation). All included subjects completed the study. Subject characteristics are shown in Table 1. The trial was performed between March and December 2013.

Table 1. Characteristics of healthy subject

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Age (years)</th>
<th>BMI (kg/m²)</th>
<th>HbA₁c (%)</th>
<th>HbA₁c (mmol/mol)</th>
<th>Fasting glucose (mmol/L)</th>
<th>Fasting insulin (pmol/L)</th>
<th>Sleep parameters from diary</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>8</td>
<td>23</td>
<td>22</td>
<td>5.2</td>
<td>34</td>
<td>5.0</td>
<td>40</td>
<td>23:48 ± 00:13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(21-24)</td>
<td>(22-23)</td>
<td>(5.1-5.5)</td>
<td>(33-37)</td>
<td>(4.8-5.0)</td>
<td>(12-62)</td>
<td>08:02 ± 00:06</td>
</tr>
</tbody>
</table>

Sleep onset (hh:mm) 23:48 ± 00:13
Sleep end (hm:mm) 08:02 ± 00:06

Glucose, insulin and C-peptide
In the healthy men, fasting and postprandial glucose levels were not different between bright and dim light (Fig. 2A). The glucose iAUC was borderline increased after exposure to bright light compared to dim light (Table 2). Fasting and postprandial insulin and c-peptide levels were not different between bright and dim light (Fig. 2B and 2C, Table 2). Also beta cell function and insulin sensitivity, as assessed with the C-peptide minimal model and oral glucose minimal model respectively, were not different between bright and dim light (see online supplemental materials).

Triglycerides and FFA
In the healthy men, fasting triglyceride levels and the postprandial triglyceride AUC were higher in bright light compared to dim light. The postprandial triglyceride iAUC did not differ between bright and dim light (Fig.2D). Fasting and postprandial FFA levels were not affected by bright light compared to dim light (Fig. 2E).

Heart rate variability
Continuous holter ECG recordings were obtained in both conditions for 7 out of 8 subjects, recordings for one subject were missing due to a technical problem. Heart rate showed a different change over time between bright and dim light (Interaction, P=0.001; Light, P=0.897), but there was no significant difference between groups at any individual time point (Fig. 2F). The LF/HF ratio also showed a different change over time between bright and dim light (Interaction, P=0.007; Light, P=0.335). Analyzing individual time points, LF/HF ratio was increased in bright light compared to dim light in the first (P=0.018) and fifth hour (P=0.028) after lights on (Fig. 2G).
Figure 2. In healthy men, bright light did not affect plasma glucose levels but increased fasting and postprandial triglyceride levels. Fasting and postprandial A glucose, B insulin, and C C-peptide levels were not different between bright light and dim light. D Fasting and postprandial triglyceride levels were elevated due to exposure to bright light compared to dim light. E Free fatty acid levels did not differ between bright light and dim light. F Heart rate did not differ between bright light and dim light in healthy men. G LF/HF ratio was slightly increased in bright light compared to dim light. Data are shown as means ± SEM of 8 subjects per group. Asterisks indicate P<0.05. Open circles are bright light and closed circles are dim light. The dashed line represents mealtime, the shaded area indicates lights off.
### Table 2. Metabolic effects of light in healthy men

<table>
<thead>
<tr>
<th></th>
<th>Dim</th>
<th>Bright</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glucose</strong></td>
<td>Fasting (mmol/L)</td>
<td>4.8 ± 0.1</td>
<td>4.8 ± 0.1</td>
</tr>
<tr>
<td></td>
<td>AUC (mmol.min/L)</td>
<td>1555 ± 47</td>
<td>1590 ± 46</td>
</tr>
<tr>
<td></td>
<td>iAUC (mmol.min/L)</td>
<td>39 ± 40</td>
<td>82 ± 37</td>
</tr>
<tr>
<td><strong>Insulin</strong></td>
<td>Fasting (pmol/L)</td>
<td>54 (38-64)</td>
<td>57 (47-62)</td>
</tr>
<tr>
<td></td>
<td>AUC (nmol.min/L)</td>
<td>55 (46-89)</td>
<td>67 (55-76)</td>
</tr>
<tr>
<td></td>
<td>iAUC (nmol.min/L)</td>
<td>41 (28-71)</td>
<td>50 (37-58)</td>
</tr>
<tr>
<td><strong>C-peptide</strong></td>
<td>Fasting (ng/L)</td>
<td>515 (428-609)</td>
<td>505 (463-555)</td>
</tr>
<tr>
<td></td>
<td>AUC (μg.min/L)</td>
<td>332 (274-399)</td>
<td>342 (286-404)</td>
</tr>
<tr>
<td></td>
<td>iAUC (μg.min/L)</td>
<td>172 (130-216)</td>
<td>190 (136-230)</td>
</tr>
<tr>
<td><strong>Triglyceride</strong></td>
<td>Fasting (mmol/L)</td>
<td>0.71 (0.55-0.92)</td>
<td>0.88 (0.63-1.07)</td>
</tr>
<tr>
<td></td>
<td>AUC (mmol.min/L)</td>
<td>307 (220-423)</td>
<td>354 (301-404)</td>
</tr>
<tr>
<td></td>
<td>iAUC (mmol.min/L)</td>
<td>65 (44-163)</td>
<td>90 (42-128)</td>
</tr>
<tr>
<td><strong>FFA</strong></td>
<td>Fasting (mmol/L)</td>
<td>0.23 (0.15-0.29)</td>
<td>0.28 (0.15-0.43)</td>
</tr>
<tr>
<td></td>
<td>Area above the curve (mmol.min/L)</td>
<td>54 (37-112)</td>
<td>65 (43-114)</td>
</tr>
</tbody>
</table>

Normally distributed data are expressed as means ± SEM, not-normally distributed data are expressed as median (25th percentile-75th percentile).

### Table 3. Characteristics of patients with type 2 diabetes

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60</td>
<td>(54-63)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>30</td>
<td>(28-35)</td>
</tr>
<tr>
<td>HbA₁c (%)</td>
<td>6.8</td>
<td>(6.7-8.0)</td>
</tr>
<tr>
<td>HbA₁c (mmol/mol)</td>
<td>51</td>
<td>(50-65)</td>
</tr>
<tr>
<td>Fasting glucose (mmol/L)</td>
<td>8.4</td>
<td>(6.2-10)</td>
</tr>
<tr>
<td>Fasting insulin (pmol/L)</td>
<td>119</td>
<td>(111-184)</td>
</tr>
</tbody>
</table>

Medication (n (%))

- **Metformin** | 8 (100)
- Lipid-lowering drugs | 4 (50)
- Anti-hypertensives | 3 (37.5)
- Proton pump inhibitor | 1 (12.5)

Sleep parameters from diary

- Sleep onset (hh:mm) | 00:05 ± 00:07
- Sleep end (hh:mm)  | 07:40 ± 00:10

* Metformin discontinued 3 days prior to each admission. Normally distributed data are expressed as mean ± SEM; nonnormally distributed data are expressed as median (25th-75th percentile).
Men with type 2 diabetes

Participants
For the type 2 diabetes patient trial, 26 subjects were screened and 8 subjects were included (17 subjects did not meet inclusion criteria, 1 subject declined participation). All included subjects completed the study. The type 2 diabetes patient trial was performed between January and July 2014. Subject characteristics are shown in Table 3.

Glucose, insulin, C-peptide, glucagon and cortisol
In the men with type 2 diabetes, fasting plasma glucose levels were elevated in bright light compared to dim light. The glucose AUC was increased after exposure to bright light compared to dim light, and the iAUC showed a similar trend (Fig. 3A and Table 4). Fasting and postprandial levels of insulin (Fig. 3B) and C-peptide (Fig. 3C) were not significantly different between bright and dim light. The C-peptide minimal model showed that the static time constant $k_g$ was lower in bright light compared to dim light (bright $1437 \times 10^{-9}$ kg/min, dim $1564 \times 10^{-9}$ kg/min, $P=0.04$), indicating reduced static insulin production in bright light. The dynamic time constant $k_d$ was not different between bright light and dim light. Insulin sensitivity as assessed with the oral glucose minimal model was not different between bright light and dim light (see online supplemental materials for details). Fasting and postprandial plasma glucagon levels (Fig. 3D), and fasting and postprandial saliva cortisol levels (Table 4) were not different between bright and dim light.

Triglycerides and FFA
In the men with type 2 diabetes, fasting plasma triglyceride levels were not different between bright and dim light, but the postprandial levels were increased in bright light compared to dim light (Fig. 3E and Table 4). Fasting and postprandial FFA levels were not affected by light (Fig. 3F and Table 4).

Appetite scores
Before lights on, the hunger, prospective food consumption, fullness and satiety scores did not differ between bright light and dim light. After lights on, fasting hunger and prospective food consumption scores were significantly higher in bright light compared to dim light. Five hours postprandially, hunger and prospective food consumption scores were significantly elevated in bright light while fullness and satiety scores were significantly decreased in bright light compared to dim light (Fig. 4).

Heart rate variability
Heart rate was increased in bright light compared to dim light (Interaction, $P<0.0001$; Light, $P<0.0001$), especially over the last three hours (Fig. 3G). The LF/HF ratio showed a trend towards increase in bright light compared to dim light (Interaction, $P<0.0001$; Light, $P=0.056$), with a significant difference in the fifth hour after lights on ($P=0.017$) (Fig. 3H).
Figure 3. In men with type 2 diabetes, bright light increased fasting and postprandial glucose levels and postprandial triglyceride levels. A Fasting and postprandial glucose levels were elevated due to exposure to bright light compared to dim light. E Postprandial triglyceride levels were also elevated due to bright light. However, fasting and postprandial B insulin, C C-peptide, D glucagon, and F free fatty acid levels did not differ between bright and dim light. G Heart rate was increased in bright light compared to dim light. H LF/HF ratio was slightly increased in bright light compared to dim light. Data are shown as means ± SEM of 8 subjects per group. Asterisks indicate P<0.05. Open circles are bright light and closed circles are dim light. The dashed line represents mealtime, the shaded area indicates lights off.
Table 4. Metabolic effects of light in men with type 2 diabetes

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>Dim</th>
<th>Bright</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose Fasting (mmol/L)</td>
<td>7.6 ± 0.7</td>
<td>8.4 ± 0.8</td>
<td>0.013</td>
</tr>
<tr>
<td>AUC (mmol.min/L)</td>
<td>3194 ± 279</td>
<td>3567 ± 299</td>
<td>0.002</td>
</tr>
<tr>
<td>iAUC (mmol.min/L)</td>
<td>791 ± 80</td>
<td>932 ± 80</td>
<td>0.075</td>
</tr>
<tr>
<td>Insulin Fasting (pmol/L)</td>
<td>160 (125-193)</td>
<td>146 (107-211)</td>
<td>0.400</td>
</tr>
<tr>
<td>AUC (nmol.min/L)</td>
<td>124 (105-150)</td>
<td>124 (106-177)</td>
<td>0.161</td>
</tr>
<tr>
<td>iAUC (nmol.min/L)</td>
<td>80 (61-101)</td>
<td>88 (66-120)</td>
<td>0.123</td>
</tr>
<tr>
<td>C-peptide Fasting (ng/L)</td>
<td>905 (765-993)</td>
<td>800 (683-1005)</td>
<td>0.208</td>
</tr>
<tr>
<td>AUC (μg.min/L)</td>
<td>477 (448-624)</td>
<td>522 (464-604)</td>
<td>0.401</td>
</tr>
<tr>
<td>iAUC (μg.min/L)</td>
<td>272 (168-304)</td>
<td>258 (222-357)</td>
<td>0.208</td>
</tr>
<tr>
<td>Glucagon Fasting (ng/L)</td>
<td>128 (85-150)</td>
<td>124 (109-152)</td>
<td>0.123</td>
</tr>
<tr>
<td>AUC (μg.min/L)</td>
<td>38.5 (32.0-49.7)</td>
<td>40.6 (34.1-50.0)</td>
<td>0.161</td>
</tr>
<tr>
<td>iAUC (μg.min/L)</td>
<td>3.5 (0.3-4.6)</td>
<td>0.6 (-3.0-4.1)</td>
<td>0.484</td>
</tr>
<tr>
<td>Triglyceride Fasting (mmol/L)</td>
<td>1.40 (1.28-1.62)</td>
<td>1.66 (1.27-2.46)</td>
<td>0.161</td>
</tr>
<tr>
<td>AUC (mmol.min/L)</td>
<td>580 (504-661)</td>
<td>797 (509-926)</td>
<td>0.012</td>
</tr>
<tr>
<td>iAUC (mmol.min/L)</td>
<td>97 (75-158)</td>
<td>124 (104-262)</td>
<td>0.012</td>
</tr>
<tr>
<td>FFA Fasting (mmol/L)</td>
<td>0.44 (0.26-0.66)</td>
<td>0.54 (0.35-0.69)</td>
<td>0.233</td>
</tr>
<tr>
<td>Area above the curve (mmol.min/L)</td>
<td>80 (42-113)</td>
<td>87 (58-114)</td>
<td>0.575</td>
</tr>
<tr>
<td>Cortisol Fasting (nmol/L)</td>
<td>6.80 ± 0.91</td>
<td>7.32 ± 1.51</td>
<td>0.691</td>
</tr>
<tr>
<td>AUC (nmol.min/L)</td>
<td>1414 ± 169</td>
<td>1541 ± 185</td>
<td>0.313</td>
</tr>
<tr>
<td>iAUC (nmol.min/L)</td>
<td>804 ± 169</td>
<td>931 ± 185</td>
<td>0.313</td>
</tr>
</tbody>
</table>

Normally distributed data are expressed as means ± SEM, not-normally distributed data are expressed as median (25th percentile-75th percentile).
Figure 4. In men with type 2 diabetes, bright light increased appetite scores. During fasting and five hours postprandially, A hunger and B prospective food consumption scores were elevated in bright light compared to dim light. C Fullness and D satiety scores were significantly decreased in bright light compared to dim light five hours postprandially. Data are shown as means ± SEM. Asterisks indicate P<0.05. Open circles are bright light and closed circles are dim light. The dashed line represents mealtime, the shaded area indicates lights off.
Discussion

In the present study, in healthy men bright light did not affect plasma glucose levels, but increased fasting and postprandial plasma triglyceride levels. In men with type 2 diabetes, bright light increased fasting and postprandial glucose levels, postprandial triglyceride levels and appetite scores.

Bright light increased fasting glucose levels in men with type 2 diabetes which is due to either increased endogenous glucose production and/or decreased tissue glucose uptake during the first hour of bright light. Animal data suggest that bright light may increase hepatic glucose production, because in rats bright light caused increased expression of liver PEPCK, a rate-limiting gluconeogenetic enzyme (8). This effect of light on PEPCK was mediated by the autonomic nervous system (8), which is in line with other studies indicating that increased sympathetic signaling increases hepatic glucose production (34, 35). Since in our study, bright light increased heart rate and tended to increase LF/HF ratio in men with type 2 diabetes we hypothesize that also in men with type 2 diabetes the light signal is transmitted from the brain to the liver via the autonomic nervous system. In addition to the potential role of the autonomic nervous system, we considered the glucocorticoid hormone cortisol as a candidate to transfer the light signal from the brain to the liver, because bright light increases glucocorticoid release via the SCN in rodents (36). Human studies investigating the effects of bright morning light on cortisol yielded conflicting results, with some studies showing increased cortisol levels after morning bright light (37, 38), whereas other studies showed no change in cortisol (39) or decreased cortisol levels due to bright light (40). Since we did not find an effect of bright light on saliva cortisol levels in the men with type 2 diabetes, cortisol is probably not involved in the effects of bright light on fasting plasma glucose in the men with type 2 diabetes.

Bright light also increased postprandial glucose levels in men with type 2 diabetes, which is at least partly explained by reduced beta cell glucose sensitivity in bright light, as indicated by the static component of the C-peptide minimal model. Since increased sympathetic signaling towards the pancreas is thought to decrease insulin secretion (41), increased sympathetic activity during bright light could explain the decreased postprandial insulin secretion in men with type 2 diabetes. We observed no changes in whole body insulin sensitivity as assessed with the oral glucose minimal model that could explain the difference in postprandial plasma glucose between bright light and dim light. Furthermore, the pancreatic hormone glucagon was not affected by bright light, and therefore not responsible for the increased glucose levels in bright light. Since we did not use a meal tracer, we cannot rule out that altered intestinal carbohydrate absorption (42) is partly responsible for the increased postprandial glucose levels in bright light in our study.

A recent study on the effects of morning exposure to blue enriched room light (260 lux) compared to dim light (<20 lux) described no changes in plasma glucose, but increased postprandial insulin levels due to blue enriched room
light (18). The discrepancy between this published effect on insulin and our healthy subject data showing no effect of morning bright light on postprandial insulin levels, may be due to differences in light intensity and wavelength, since we recently observed intensity- and wavelength-dependent effects of light on glucose tolerance in rodents (unpublished observations). Our second study provides the first evidence that bright light can actually affect plasma glucose levels in men with type 2 diabetes.

We performed two separate trials in different populations, and the trials were not designed to make a direct comparison between healthy men and obese men with type 2 diabetes. The study populations differ in age, bodyweight and plasma glucose levels. Differences in outcome parameters between the study populations may be attributed to one or more of these factors. It is however interesting to observe that the effects of bright light on triglycerides are similar between studies. Fasting triglyceride levels were significantly increased due to bright light in healthy men and showed a similar trend in men with type 2 diabetes. Elevated fasting triglyceride levels are due to either increased hepatic VLDL secretion or decreased tissue triglyceride uptake during the first hour of bright light. Since increased sympathetic signaling is known to increase hepatic VLDL secretion (43) and we observed increased sympathetic activity due to bright light, increased VLDL secretion due to increased hepatic sympathetic signaling is a possible explanation for the observed increased fasting triglyceride levels. For postprandial triglyceride levels, increased intestinal absorption may be an additional contributing factor, given that the SCN controls intestinal lipid absorption (44) and bright light affects human gastrointestinal motility (42). Our data suggest that the increased plasma triglyceride levels may persist for longer after the meal in the men with type 2 diabetes compared to the healthy men, which may be related to a prolonged intestinal transit time in patients with type 2 diabetes (45).

The observed effects of bright light on appetite in men with type 2 diabetes contrast to a recent study showing no effect of exposure to morning blue-enriched light on appetite (18), which may again be related to differences in light intensity, wavelength or subject gender, between the study by Cheung et al and our study. The underlying pathway through which light affects appetite remains speculative. Appetite is controlled by a complex interplay of hormones, neurotransmitters and neuropeptides (46). The hypothalamic neuropeptide orexin is a candidate, since orexin neurons are activated by light, and orexin increases appetite as well as sympathetic tone (47). The physiological role of increased appetite, plasma glucose and triglyceride levels due to bright light exposure in the morning may be to mobilize energy in order to prepare the body for physical activity.

A limitation of our experimental setup is the absence of a fasting plasma sample before lights on. The cannula was inserted after lights on for two reasons. First, in order to prevent sleep disturbance due to the presence of a cannula, the cannula was not inserted in the evening. Second, in order to prevent a difficult insertion procedure in the dark or in dim red light, with resulting subject stress,
the cannula was not inserted before lights on in the morning. However, despite
the absence of a baseline measurement before lights on, we are confident that
the observed changes in glucose and triglyceride metabolism are due to light,
since all subjects were studied twice in a random order, and all conditions except
light exposure remained constant between bright light and dim light.

The potential clinical implications of our findings are twofold. First, fasting glucose
is a main clinical criterion for the diagnosis of type 2 diabetes (20) and fasting
triglyceride levels can be used to assess cardiovascular risk (48). We observed
a difference between 10 lux and 4000 lux light exposure in fasting triglyceride in
healthy men and in fasting glucose in men with type 2 diabetes. Therefore, our
data warrant further investigation of the effects of intermediate light intensities
on fasting plasma glucose and triglyceride levels and the practical implications
for diagnostic blood sampling. Second, in the treatment of patients with type
2 diabetes, strategies to reduce HbA1c are effective to reduce microvascular
and cardiovascular complications (49). Fasting and postprandial glucose levels
together determine HbA1c levels (50), and were acutely elevated due to bright
light exposure in our study. In addition, in a non-controlled environment increased
appetite due to bright light exposure will likely cause increased food intake. Thus,
our results suggest that optimization of ambient light exposure is a potential
strategy to reduce glycemia in patients with type 2 diabetes. Furthermore, if the
observed effects of light exposure during the day (the appropriate phase) can be
translated to the night (the inappropriate phase), our data suggest that ambient
light may have a causal contribution to the observed correlations between
nocturnal light exposure and metabolic disorders (9-12). However, the metabolic
effects of bright light at other times across the 24-hr cycle, the metabolic effects
of other light intensities and wavelengths, and the long-term effects of modified
ambient light exposure on the prevention and treatment of hyperglycemia and
dyslipidemia need to be evaluated in future clinical trials. It is important to
note that long-term effects may differ from acute effects, as suggested by two
case reports showing an improvement of insulin sensitivity with morning light
treatment in patients with seasonal affective disorder and insulin dependent
diabetes (16, 17).

In conclusion, we showed that bright morning light increases plasma triglyceride
levels in healthy men, and increases plasma triglyceride and glucose levels in
obese men with type 2 diabetes. Our data support the concept that ambient light
can directly modulate human plasma glucose and triglyceride levels.
References


Supplemental data

Oral glucose minimal model

Description of the model

The glucose minimal model for intravenous glucose tolerance tests (IVGTT) was introduced in 1979 (S1). Later this model was extended to the oral glucose minimal model, designed for oral glucose tolerance or mixed meal tests (S2). The minimal model was validated in healthy subjects against the intravenous glucose tolerance test (S3), oral tracer method (S4) and euglycemic hyperinsulinemic clamp (S5) and in subjects with impaired glucose tolerance against the euglycemic hyperinsulinemic clamp (S5). The model comprises two coupled ordinary differential equations. The first describes the glucose concentration, \( G(t) \), in plasma as a function of time after a glucose dose at time \( t=0 \):

\[
\frac{dG(t)}{dt} = S_g(G_b - G(t)) - X(t)G(t) + \frac{R(t)}{BW} \quad G(0) = G_0
\]  

(1)

where \( S_g \) is a parameter that describes the ‘glucose effectiveness’, the glucose utilization that is independent the insulin concentration, \( BW \) is the body weight, \( G_b \) the basal glucose concentration and \( R(t) \) a function describing the appearance of glucose in the plasma. The second equation describes the insulin ‘action’, \( X(t) \), the effect of insulin on the glucose utilization:

\[
\frac{dX(t)}{dt} = p_3(I(t) - I_b) - p_2X(t) \quad X(0) = 0
\]  

(2)

Where \( I_b \) is the basal insulin concentration and the parameters \( p_2 \) and \( p_3 \) define the insulin sensitivity \( S_I = p_3/p_2 \). \( I(t) \) is the measured insulin concentration and is used as a ‘forcing function’ in the model.

The rate of appearance of glucose in the plasma, \( R(t) \), is modeled with a piecewise linear function (S2)

\[
R(t) = \alpha_{i-1} + \frac{\alpha_i - \alpha_{i-1}}{t_i - t_{i-1}} (t - t_{i-1}) \quad \text{for} \quad t_{i-1} < t < t_i
\]  

(3)

with parameters \( \alpha_i \). The function \( R(t) \) was chosen to have eight parameters \( \alpha_i \) (i=1..8) corresponding to the breakpoints in \( R(t) \) (S2, S6). The breakpoints are located at \( t=0, 10, 30, 60, 90, 120, 180, 300 \) minutes after the glucose dose.
Modeling
Glucose and insulin concentrations were obtained as described in the main text. Estimates for the parameters of the minimal model were calculated by minimizing the objective function

\[ E = \frac{\sum_i (g(t_i) - \hat{g}(t_i))^2}{\sigma_i^2} \]  

(4)

Where \( g(t_i) \) and \( G(t_i) \) are the measured and model values of the glucose concentration at time \( t_i \), respectively. \( \sigma_i \) is the error in the measured glucose concentration and was estimated at 2%. The minimization was done with the Matlab (version 2013b) GlobalSearch algorithm followed by a grid search for the parameters \( p_2 \) and \( p_3 \) while keeping the other parameters fixed at the values found with the GlobalSearch algorithm. The parameter \( S_g \) was kept fixed at \( S_g = 0.031 \) (S4). We checked the consistency of this value for \( S_g \) by fitting the model with \( S_g \) as a free parameter while keeping the other parameters fixed. For the healthy men as well as the men with type 2 diabetes the best estimate for \( S_g \) was within 10% of the fixed value of \( S_g = 0.031 \).

In a first analysis, we used the individual glucose and insulin concentrations as model input data. This resulted in a large individual variation in the parameter values. Therefore, we decided to use the average concentration profiles, as described previously by Dalla Man et al. (S7). For both studies, the average glucose and insulin concentration profiles were calculated for bright and dim light by taking the average concentration over all subjects at each time point and we used the average bodyweight, \( BW \), of the subjects. Differences between the groups were assessed using P-values obtained from a z-test using the dependent confidence intervals to estimate the standard errors (S8, S9).

Results: Healthy men
Supplemental Table 1 lists the best estimates and P-values for the parameters \( p_2 \), \( p_3 \) and the insulin sensitivity \( S_I \). The parameters are not different between bright and dim light. The measured and modeled data points from the healthy men are shown in Supplemental Figure 1.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Best estimate</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( p_2 ) (min(^{-1}))</td>
<td>Dim 0.06</td>
<td>Bright 0.08</td>
</tr>
<tr>
<td>( p_3 ) (L/pmol min(^2))</td>
<td>Dim 3.1 \times 10^{-6}</td>
<td>Bright 3.0 \times 10^{-6}</td>
</tr>
<tr>
<td>( S_I ) (L/pmol min)</td>
<td>Dim 5.2 \times 10^{-5}</td>
<td>Bright 3.8 \times 10^{-5}</td>
</tr>
</tbody>
</table>

Supplemental Table 1. The best estimates for glucose minimal model parameters \( p_2 \), \( p_3 \) and the insulin sensitivity \( S_I \) in healthy men. P-values are calculated with a z-test using the dependent confidence interval (S8, S9). The rate of appearance function was modeled through a piecewise linear function with eight parameters, \( \alpha_i \), \( i = 1...8 \). The best estimates of the parameters \( \alpha_i \) for dim light are: \( \alpha_1 = 0.4 \), \( \alpha_2 = 8.0 \), \( \alpha_3 = 12.1 \), \( \alpha_4 = 4.6 \), \( \alpha_5 = 8.2 \), \( \alpha_6 = 4.2 \), \( \alpha_7 = 1.6 \), \( \alpha_8 = -0.8 \). For bright light the best estimates for the piecewise linear function parameters are: \( \alpha_1 = -1.0 \), \( \alpha_2 = 13.1 \), \( \alpha_3 = 7.5 \), \( \alpha_4 = 5.1 \), \( \alpha_5 = 6.8 \), \( \alpha_6 = 3.7 \), \( \alpha_7 = 1.1 \), \( \alpha_8 = -0.6 \).
Results: Men with type 2 diabetes
The parameters $p_2$, $p_3$ and the insulin sensitivity $S_I$ obtained from the men with type 2 diabetes are shown in Supplemental Table 2. It should be noted that in the men with type 2 diabetes the best estimate for the parameter $p_3$ was $p_3 = 0$, and consequently, $S_I = 0$, for four out of the five best fit runs. This was the case for dim and bright light. The measured average glucose concentrations and the values calculated with the glucose minimal model are shown in Supplemental Figure 2.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Dim</th>
<th>Bright</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$p_2$ (min$^{-1}$)</td>
<td>0.012</td>
<td>0.04</td>
<td>0.2</td>
</tr>
<tr>
<td>$p_3$ (L/pmol min$^2$)</td>
<td>$4.5 \times 10^{-9}$</td>
<td>$15 \times 10^{-9}$</td>
<td>0.5</td>
</tr>
<tr>
<td>$S_I$ (L/pmol min)</td>
<td>$3.7 \times 10^{-7}$</td>
<td>$3.8 \times 10^{-7}$</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Supplemental Table 2. Best estimates for the glucose minimal model parameters $p_2$, $p_3$, and the insulin sensitivity $S_I$ for men with type 2 diabetes. The P-values are calculated with a z-test using the dependent confidence interval (S8, S9). The rate of appearance function, $R(t)$, was modeled with a piecewise linear function with eight parameters, $\alpha_i$, $i=1...8$. The best estimates of the parameters $\alpha_i$ for dim light are: $\alpha_1=3.1$, $\alpha_2=21.2$, $\alpha_3=16.1$, $\alpha_4=20.8$, $\alpha_5=15.0$, $\alpha_6=14.9$, $\alpha_7=3.0$, $\alpha_8=-5.9$. For bright light the best estimates for parameters of the piecewise linear function are $\alpha_1=3.5$, $\alpha_2=16.4$, $\alpha_3=19.8$, $\alpha_4=22.1$, $\alpha_5=22.6$, $\alpha_6=14.0$, $\alpha_7=5.7$, $\alpha_8=-5.6$. 
Supplemental Figure 2. Data and fit for average concentration profiles of glucose for men with type 2 diabetes. The left panel shows the data (filled symbols) and model (open symbols) for dim light; the right panel for bright light. The parameter values used for the fits are given in Supplemental Table 2.

The C-peptide minimal model

Model description

Modelling insulin concentration in plasma is notoriously difficult because the liver clears part of the secreted insulin before it can enter the systemic circulation. Since C-peptide passes the liver unhindered, C-peptide secretion is used as a representation of pancreatic insulin secretion. The two component model (S10) for C-peptide concentrations in plasma has been successfully used to model C-peptide concentrations in hyperglycemic clamps as well as in meal and intravenous glucose challenge tests (S6, S11, S12, S13) in normal individuals and individuals with impaired glucose tolerance. The model comprises two compartments, a central compartment in rapid equilibrium with plasma and a peripheral compartment that is not readily accessible. The equations governing the plasma concentrations in both compartments describe a simple distribution of C-peptide over both compartments (parameters $k_1$ and $k_2$ below) and the decay of C-peptide from the plasma (parameter $k_c$):

\[
\frac{dC(t)}{dt} = -(k_c + k_1)C(t) + k_2Y(t) + \frac{S(t)}{BW} \quad C(0) = C_0
\]

\[
\frac{dY(t)}{dt} = k_1 C(t) - k_2 Y(t) \quad Y(0) = \frac{k_2}{k_1} C(0)
\]

where $C(t)$ and $Y(t)$ are the plasma and peripheral C-peptide concentrations in pmol/L as a function of time, respectively; $BW$ is the body weight in kilograms and $C_0$ is the measured C-peptide concentration at time $t = 0$. We use the insulin release function described previously by Breda et al. (S12):

\[
S(t) = S_s(t) + S_d(t)
\]
This function models the entry of C-peptide into the plasma in pmol per minute. The static component, $S_s(t)$, which probably represents the production of new insulin granules, is assumed to equilibrate with a time constant $T$ towards a state proportional to the glucose concentration, $G(t)$, above the threshold level $h$ (S6, S11, S12). $k_g$ is the static responsivity index (S6) that measures the secreted C-peptide per minute in response to the glucose concentration above the threshold $h$:

$$S_s(t) = y(t)$$ (8)

with

$$\frac{dy(t)}{dt} = -\frac{1}{T} (y(t) - k_g(G(t) - h))$$ (9)

The dynamic component of $S(t)$, $S_d(t)$, probably represents exocytosis of docked insulin granules and is proportional to the change in glucose concentration:

$$S_d(t) = k_d \frac{dG(t)}{dt} \quad \text{for} \quad \frac{dG(t)}{dt} > 0 \quad \text{and} \quad S_d(t) = 0 \quad \text{for} \quad \frac{dG(t)}{dt} < 0$$ (10)

Where $k_d$ is the dynamic responsivity index. The parameters $k_\gamma$, $k_\alpha$, and $k_\zeta$ were kept fixed at values measured by De Cauter et al. (S14) ($k_c = 0.062$, $k_1 = 0.053$, $k_2 = 0.051$ for the healthy men and $k_c = 0.064$, $k_1 = 0.069$, $k_2 = 0.053$ for the men with type 2 diabetes). The measured glucose- and C-peptide plasma concentrations were used to estimate the model parameters $k_g$, $h$, and $k_d$ by minimizing the residual error between the measured and modeled C-peptide concentration. The residual error is the sum of squares of the difference between the modeled and the measured C-peptide concentration:

$$E = \frac{\sum(t_i)(c(t_i) - \hat{c}(t_i))^2}{\sigma_i^2}$$ (11)

where the $t_i$ denote the time points at which the data were obtained, $C(t)$ the model C-peptide concentration at time $t$, $c(t)$ the measured C-peptide concentration at $t$, and $\sigma_i$ the estimated error in the measured C-peptide concentration. The measurement error was estimated at 6%.

**Modeling**

The minimization of the error function was done with the Matlab (version 2013b) GlobalSearch algorithm followed by a manual grid search to further refine the parameter values.

The study in the healthy men and the study in the men with type 2 diabetes were analyzed separately. For each study, the average C-peptide and glucose
concentration profiles were calculated for bright and dim light by taking the average concentration over all subjects at each time point; the average bodyweight, $BW$, for the subjects in the study was used. In a separate analysis, the individual C-peptide and glucose concentrations were used as model input. This showed a large individual variation in the parameter values, and therefore we decided to use average concentration profiles, as described previously by Breda et al. (S12).

We found that it was not possible to consistently determine the time constant $T$ (equation [9]) from the data, which is consistent with data in the literature (S11). Therefore, we assume that at the time scale of the measurements, $dy(t)/dt = 0$ and that the static component $S_z(t) = k_g(G(t) - h)$.

To determine the significance of the differences between the parameters in dim and bright light we calculated the standard error for each parameter while keeping the remaining parameters values at their best estimates (S8, S9). A $z$-test was used to calculate the P-value for the null hypothesis that there is no difference in the parameter values between dim and bright light.

**Results: Healthy men**

The results of fitting the parameters $k_g, h$ and $k_d$ are listed in Supplemental Table 3 and the model fits are shown in Supplemental Figure 3. The parameters are not different between dim and bright light.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Best estimate</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$kg$ (kg/min)</td>
<td>Dim: $10053 \times 10^{-9}$; Bright: $9821 \times 10^{-9}$</td>
<td>0.4</td>
</tr>
<tr>
<td>$h$ (mmol/L)</td>
<td>Dim: 4.42; Bright: 4.47</td>
<td>0.2</td>
</tr>
<tr>
<td>$kd$ (kg)</td>
<td>Dim: $10000 \times 10^{-9}$; Bright: $17667 \times 10^{-9}$</td>
<td>0.4</td>
</tr>
</tbody>
</table>

**Supplemental Table 3.** C-peptide model parameters $kg, h$ and $kd$ of function $S(t)$ for the healthy men. The values for model parameters $kc, k_1$ and $k_2$ were taken from (S14): $kc = 0.062$, $k_1 = 0.053$ and $k_2 = 0.051$. The P-values were calculated from a $z$-test using the dependent confidence intervals (S8, S9).

**Supplemental Figure 3.** Data and fit for average concentration profiles of C-peptide for the healthy men. The left panel shows the measured data (filled symbols, connected with a line) and model data (open symbols) for dim light, the right panel shows the data for bright light. The parameter values used for the fits are given in Supplemental Table 3.
Results: Men with type 2 diabetes
The best estimates of the model parameters $k_g$, $h$ and $k_d$ for the men with type 2 diabetes are listed in Supplemental Table 4. Supplemental Figure 4 shows the model fit to the data. The static responsivity index $kg$ is higher in dim light ($p = 0.04$) compared to bright light. The dynamic responsivity $kd$ and the threshold $h$ are not different between bright and dim light.

Supplemental Table 4. Best estimates for the C-peptide model parameters $k_g$, $h$ and $kd$ for the men with type 2 diabetes. The model parameters $k_c$, $k_1$ and $k_2$ were taken from (S14). These are $k_c = 0.064$, $k_1 = 0.069$ and $k_2 = 0.053$. The P-values were calculated with a z-test using the dependent confidence intervals (S8, S9).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Dim</th>
<th>Bright</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$kg$ (kg/min)</td>
<td>$1564 \times 10^{-9}$</td>
<td>$1437 \times 10^{-9}$</td>
<td>0.04</td>
</tr>
<tr>
<td>$h$ (mmol/L)</td>
<td>3.29</td>
<td>3.37</td>
<td>0.4</td>
</tr>
<tr>
<td>$kd$ (kg)</td>
<td>$14564 \times 10^{-9}$</td>
<td>$9025 \times 10^{-9}$</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Supplemental Figure 4. Data and fit for average concentration profiles of glucose for the men with type 2 diabetes. The left panel shows the data (filled symbols, connected with a line) and model (open symbols) for dim light; the right panel for bright light. The parameter values used for the fits are given in Supplemental Table 4.
Supplemental references


