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 $t=0$:

$$\frac{dG(t)}{dt} = S_g\left(G_b - G(t)\right) - X(t)G(t) + \frac{R(t)}{BW} \qquad G(0) = G_0 \qquad [1]$$

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:

$$\frac{dX(t)}{dt} = p_3\left(I(t) - I_b\right) - p_2X(t) \qquad X(0) = 0 \qquad [2]$$

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)

$$R(t) = \alpha_{i-1} + \frac{\alpha_i - \alpha_{i-1}}{t_i - t_{i-1}}\left(t - t_{i-1}\right) \qquad \text{for} \qquad t_{i-1} < t < t_i \qquad [3]$$

with parameters α_i. The function $R(t)$ was chosen to have eight parameters α_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

$$E = \frac{\sum_i (g(t_i) - G(t_i))^2}{\sigma_i^2} \qquad [4]$$

Where $g(t_i)$ and $G(t_i)$ are the measured and model values of the glucose concentration at time t_i, respectively. σ_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.

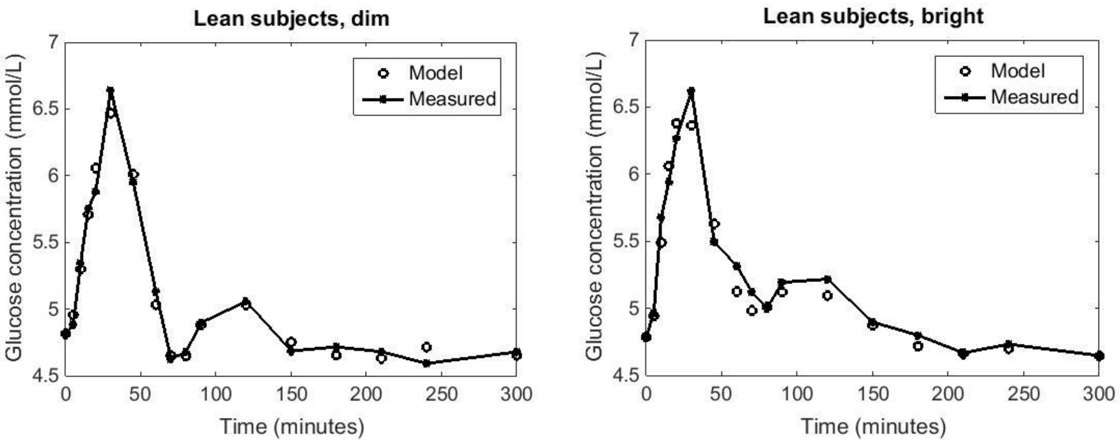
In a first analysis, we used the individual glucose and insulin concentrations as model input data. This resulted in a large individual variation in the parameter values. Therefore, we decided to use the average concentration profiles, as described previously by Dalla Man et al. (S7). For both studies, 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, 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.

	Best estimate		P-value
Parameter	Dim	Bright	
p_2 (min^{-1})	0.06	0.08	0.2
p_3 (L/pmol min^2)	3.1×10^{-6}	3.0×10^{-6}	0.5
S_I (L/pmol min)	5.2×10^{-5}	3.8×10^{-5}	0.5

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, α_i, i=1…8. The best estimates of the parameters α_i for dim light are: α_1=0.4, α_2=8.0, α_3=12.1, α_4=4.6, α_5=8.2, α_6=4.2, α_7=1.6, α_8=-0.8. For bright light the best estimates for the piecewise linear function parameters are: α_1=-1.0, α_2=13.1, α_3=7.5, α_4=5.1, α_5=6.8, α_6=3.7, α_7=1.1, α_8=-0.6.



(a) (b)

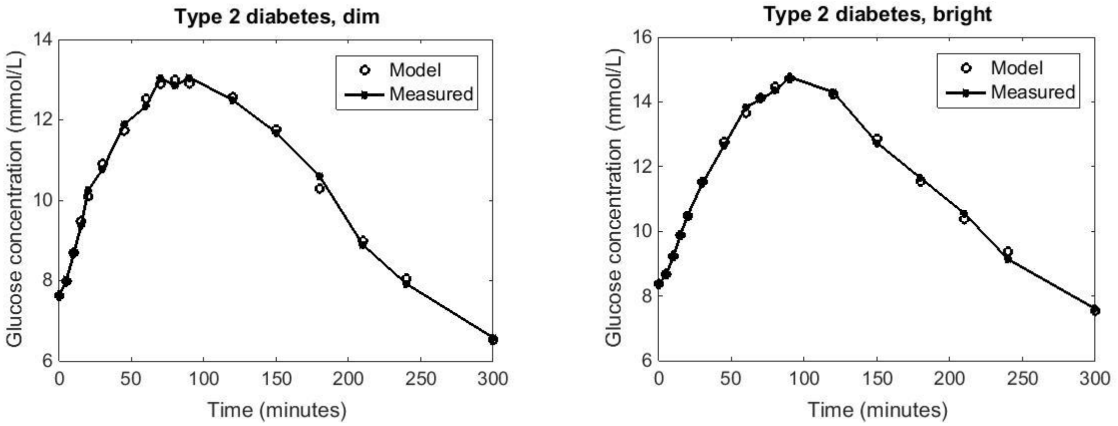
Supplemental Figure 1: Data and fit for average concentration profiles of glucose for the healthy men. The left panel shows the average measured glucose concentration (filled symbols, connected with a line) and glucose concentrations calculated with the glucose minimal model (open symbols) for dim light, the right panel for bright light. The parameter values used for the fits are given in Supplemental Table 1.

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.

	Best estimate		P-value
Parameter	Dim	Bright	
p_2 (min^{-1})	0.012	0.04	0.2
p_3 (L/pmol min^2)	4.5×10^{-9}	15×10^{-9}	0.5
S_I (L/pmol min)	3.7×10^{-7}	3.8×10^{-7}	0.3

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, α_i, i=1…8. The best estimates of the parameters α_i for dim light are: α_1=3.1, α_2=21.2, α_3=16.1, α_4=20.8, α_5=15.0, α_6=14.9, α_7=3.0, α_8=-5.9. For bright light the best estimates for parameters of the piecewise linear function are α_1=3.5, α_2=16.4, α_3=19.8, α_4=22.1, α_5=22.6, α_6=14.0, α_7=5.7, α_8=-5.6.



(b) (b)

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):

$$\frac{dC(t)}{dt} = -(k_c + k_1)C(t) + k_2 Y(t) + \frac{S(t)}{BW} \qquad C(0) = C_0 \qquad [5]$$

$$\frac{dY(t)}{dt} = k_1\, C(t) - k_2\, Y(t) \qquad Y(0) = \frac{k_2}{k_1}\, C(0) \qquad [6]$$

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):

$$S(t) = S_s(t) + S_d(t) \tag{7}$$

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:

$$S_s(t) = y(t) \tag{8}$$

with

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

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:

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

Where k_d is the dynamic responsivity index. The parameters k_1, k_2 and k_c 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:

$$E = \frac{\sum_i (c(t_i) - C(t_i))^2}{\sigma_i^2} \qquad [11]$$

where the t_i denote the time points at which the data were obtained, $C(t_i)$ the model C-peptide concentration at time t_i, $c(t_i)$ the measured C-peptide concentration at t_i and σ_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 $S_z(t) = k_g(G(t) - h)$.

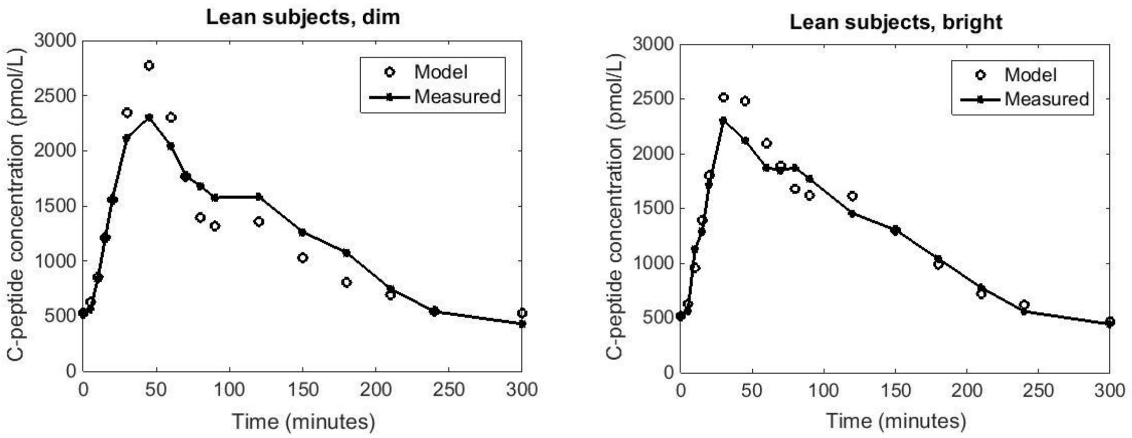
To determine the significance of the differences between the parameters in dim and bright light we calculated the standard error for each parameter while keeping the remaining parameters values at their best estimates (S8, S9). A z-test was used to calculate the P-value for the null hypothesis that there 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.

	Best estimate		P-value
Parameter	Dim	Bright	
k_g (kg/min)	10053 x 10^{-9}	9821 x 10^{-9}	0.4
h (mmol/L)	4.42	4.47	0.2
k_d (kg)	10000 x 10^{-9}	17667 x 10^{-9}	0.4

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



(a) (b)

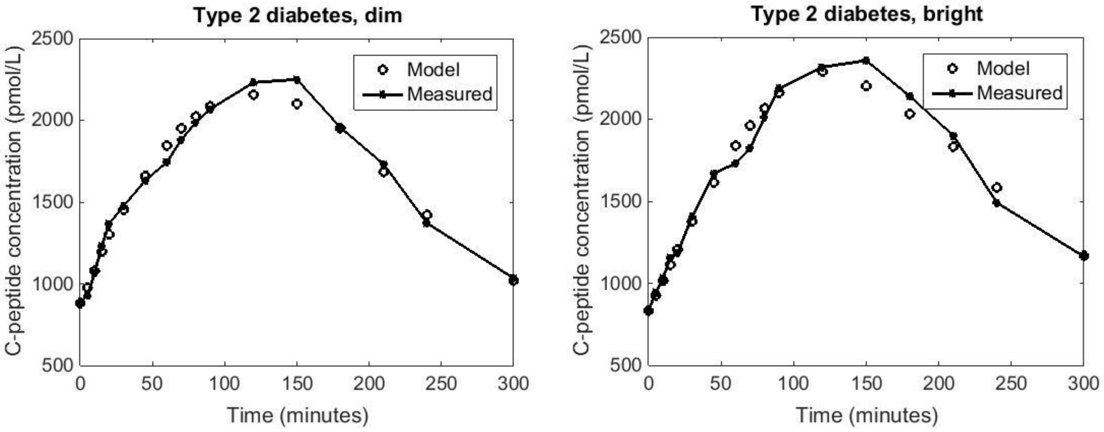
Supplemental Figure 3: Data and fit for average concentration profiles of C-peptide for the healthy men. The left panel shows the measured data (filled symbols, connected with a line) and model data (open symbols) for dim light, the right panel shows the data for bright light. The parameter values used 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 k_g is higher in dim light ($p = 0.04$) compared to bright light. The dynamic responsivity k_d and the threshold h are not different between bright and dim light.

	Best estimate		P-value
Parameter	Dim	Bright	
k_g (kg/min)	1564 x 10^{-9}	1437 x 10^{-9}	0.04
h (mmol/L)	3.29	3.37	0.4
k_d (kg)	14564 x 10^{-9}	9025 x 10^{-9}	0.2

Supplemental Table 4: Best estimates for the C-peptide model parameters kg , h and k_d for the men with type 2 diabetes. The model parameters k_C, k_1 and k_2 were taken from (S14). For Study 2 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).



(a) (b)

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.

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