ONLINE DATA SUPPLEMENT

Alterations in Glucose Disposal in Sleep-disordered Breathing

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METHODS

Study Sample

The study sample consisted of normal subjects and patients with newly diagnosed but untreated SDB. Normal subjects were recruited from the general community. Patients undergoing polysomnography and confirmed to have SDB were recruited. Subjects with a fasting glucose greater than 125mg/dl or those with a history of type 2 diabetes mellitus, angina, myocardial infarction, coronary revascularization, congestive heart failure, or stroke were excluded. In addition, history of a circadian rhythm disorder, chronic insufficient sleep (<7 hrs/night), obstructive lung disease, renal or hepatic dysfunction, upper airway surgery, cancer, or any chronic inflammatory condition was also considered exclusionary. Finally, subjects using anti-inflammatory agents (e.g., steroids), supplemental oxygen, or positive airway pressure therapy were ineligible. After the initial screening visit, those enrolled were counseled on maintaining at least seven hours of sleep per night and asked to consume at least 250g of carbohydrates per day. Usual sleep habits were objectively assessed with an ambulatory wrist activity monitor that was worn for at least five days before completion of the metabolic tests. Informed consent was obtained from all subjects and the protocol was approved by the local Institutional Review Board. From December 2003 through August 2006, a total of 79 patients with SDB and 39 community-based normal subjects were found to be eligible and agreed to participate in the study. Informed consent was obtained from all subjects and the protocol was approved by the local Institutional Review Board.

Minimal Model Analysis of the Frequently Sampled Intravenous Glucose Tolerance Test

The minimal model provides a mathematical representation of glucose disposal during the FSIVGTT using two coupled differential equations (E1-E2). The first equation represents the physiological factors that facilitate the return of glucose to basal levels after the glucose injection. These include the effects of insulin, which normalize plasma glucose through the glucose transporter system, and the effects of glucose itself which can normalize its concentration through mass action. The second

equation describes the movement of insulin from plasma into the interstitial space where it exerts its physiologic actions. The equations of the minimal model are as follows:

Equation 1: $$\frac{dG(t)}{dt} = -\{p_1 + X(t)\}G(t) + p_1 G_b$$

Equation 2: $$\frac{dX(t)}{dt} = -p_2 X(t) + p_3[I(t) - I_b]$$

where *G(t)* [mg/dl] and *I(t)* [uU/ml] represent plasma glucose and insulin levels, respectively. *X(t)* describes the effect of insulin on glucose disposal in the interstitial (or "remote") compartment and is referred to as the remote insulin concentration. *dG(t)/dt* is the glucose restoration rate and the *dX(t)/dt* is the rate of increase of insulin in the interstitial or remote compartment. G_b and I_b are basal values of plasma glucose and insulin, respectively, prior to the glucose injection. Parameter p_1 represents glucose effectiveness (S_G), which is the fractional disappearance rate of glucose independent of any insulin response. Parameters p_2 and p_3 determine the kinetics of insulin transport, respectively, into and out of the interstitial space where insulin action is expressed. S_I is calculated as p_3/p_2. Conceptually, the equations of the minimal model can be re-expressed as

Equation 1: $$\frac{dG(t)}{dt} = -\{S_G + X(t)\} * G(t)$$

Glucose Restoration Rate = - { Glucose Effectiveness - Remote Insulin } G(t)

Equation 2: $$\frac{dX(t)}{dt} = -p_2 X(t) + p_3 I(t)$$

Increase in Remote Insulin = $-p_2$ Remote Insulin + p_3 Plasma Insulin

By using the measured insulin profile during the FSIVGTT as the input to the model, the glucose concentration profile is determined by non-linear least-squares fitting and parameters of insulin-sensitivity ($S_I = p_3/p_2$) and glucose effectiveness ($S_G = p_1$) are numerically estimated. S_I quantifies the

effect of insulin in enhancing glucose disposal. S_G quantifies the effects of glucose on its own disposal independent of any insulin response. S_G quantifies the effects of glucose on its own disposal independent of any insulin response. S_G is further divided into two components: the contribution of hyperglycemia *per se* to increase glucose disposal and the effect of basal insulin levels. The basal component of S_G is referred to as the basal insulin effect (BIE) and is the product of basal insulin (I_b) and S_I. The contribution of non-insulin-dependent glucose uptake (glucose effectiveness at zero insulin, GEZI) to glucose disposal is the difference between total S_G and the BIE: GEZI = S_G - (Ib x S_I). In addition to estimating S_I, S_G, and GEZI, the acute insulin response to glucose (AIRg), an index of pancreatic beta-cell function, was also calculated as the area under the insulin curve between 0 and 10 minutes as follows:

$$\text{AIRg} = \int_{0\,\text{min}}^{10\,\text{min}} [I(t) - I_b]dt$$

Finally, the disposition index (DI), which represents the ability of the pancreatic beta-cell to compensate for insulin resistance, is calculated as the product of S_I and AIRg.

Biochemical Assays

Glucose was measured enzymatically in duplicate using a Glucose Analyzer II (Beckman Instruments, Fullerton CA). Insulin concentrations were determined in duplicate by radioimmunoassay using standard commercial kits (Linco Research; St Charles, MO).

REFERENCES

E1. Bergman RN, Ider YZ, Bowden CR, Cobelli C. Quantitative estimation of insulin sensitivity. *Am J Physiol* 1979;236:E667-E677.

E2. Bergman RN, Finegood DT, Ader M. Assessment of insulin sensitivity in vivo. *Endocr Rev* 1985;6:45-86.