**Endogenous glucose production during a 75g oral glucose load is associated with fasting serum serotonin in type 2 diabetes**

**Background**

Serotonin has been reported to modulate lipid and glucose metabolism. In mice, circulating serotonin increases endogenous glucose production (EGP). However, this phenomenon has not been examined in humans with type 2 diabetes (T2D). We assessed the relationships between EGP with serum serotonin and glucoregulatory hormones after an oral glucose load in T2D.

**Methods**

25 participants with metformin-treated T2D (18M/7F, 67.1±1.2 years, BMI 32±1.5kg/m2, HbA1c 7.0±0.1%, without medications affecting serotonin levels) were evaluated. After an overnight fast, participants received an IV bolus infusion of 6,6-[2H2]glucose (28µmol/kg) at t=-180min, followed by a continuous IV infusion at 0.28 µmol/kg/min at t=-180-240min), and a 75g glucose drink containing 1.5g [U-13C]glucose at t=-5-0min. Venous blood was sampled to measure blood glucose (glucometer), serotonin (ELISA), plasma insulin (ELISA), glucagon (radioimmunoassay) and EGP (gas chromatography-mass spectrometry). The relationship between EGP AUC0-240min with serotonin was assessed by linear regression analysis, adjusted for HbA1c, gender and BMI. Participants were stratified into ‘low’ (≤10 ng/mL N=15) or ‘high’ (>10 ng/mL, N=10) serotonin subgroups, with insulin, glucagon and EGP responses to oral glucose compared by two-way ANOVA. Data are means ± SEM.

**Results**

After the glucose drink, EGP decreased rapidly to a nadir at t=30min, followed by a progressive increase to a peak at t=150min. EGP AUC0-240min was related directly to fasting serotonin (R2=0.26, P=0.004). In participants with ‘high’ serotonin, EGP was greater (Group×Time: P=0.0003) and glucagon suppression was less (Group×Time: P=0.029) after oral glucose. Blood glucose and plasma insulin levels were comparable between the two subgroups.

**Conclusion**

In people with T2D, EGP after an oral glucose load is related to fasting serum serotonin, which may reflect impaired glucagon suppression. These observations support further investigation into the relevance of serotonin to the regulation of glucose metabolism in both health and T2D.

