

C8 and PC18

Serotonin 2C receptor agonists improve type 2 diabetes via central MC4R signaling pathways

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The burden of type 2 diabetes and its associated premature morbidity and mortality is rapidly growing, and the need for novel efficacious treatments is pressing. We have shown that serotonin 2C receptor agonists, typically investigated for their anorectic properties, significantly improve glucose and insulin tolerance in murine models of obesity and type 2 diabetes. Importantly, these improvements in glucose homeostasis occurred at concentrations of agonist which had no effect on ingestive behavior, VO₂, locomotor activity, body weight, or fat mass. We determined that this primary effect on glucose homeostasis requires downstream activation of central melanocortin-4 receptors (MC4Rs), but not MC3Rs, and is associated with MC4R-mediated stimulation of sympathetic pre-ganglionic neurons in the spinal cord, increased insulin signaling in liver and skeletal muscle, and inhibition of hepatic gluconeogenesis at the transcriptional level. These findings suggest that pharmacological targeting of 5-HT_{2C}Rs may enhance glucose tolerance independently of alterations in body weight, and that this may prove an effective and mechanistically novel strategy in the treatment of type 2 diabetes.

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Where applicable, the authors confirm that the experiments described here conform with The Physiological Society ethical requirements.

C9 and PC19

Cardiovascular autonomic responses to hyperinsulinemia in young adult males of normal and low body mass index

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Background: Hyperinsulinemia is known to increase sympathetic nervous system activity (1), although it is unclear if there is a differential response to hyperinsulinemia in individuals who range

from low to normal BMI. Low BMI is an important public health problem in the developing world, and may successful adaptations to a habitually low energy intake may result in different autonomic responses to stress. Approximately 30% of adults in developing world have low BMI (2). We therefore evaluated whether individuals of low BMI had differentiated autonomic nervous response to hyperinsulinemia during controlled laboratory conditions as compared with individuals of normal BMI. Method: 51 young men (aged 18-35 years) were divided into 2 groups based on their body mass index. Normal BMI (n=23; BMI, 18.5-24.9 Kg/m²) and the low BMI (n=28; BMI, < 18.5 Kg/m²). All subjects underwent assessment of detailed anthropometry, physical activity levels (PAL) and euglycemic hyperinsulinemic clamp (HEC) (3). Lead II ECG and beat to beat blood pressure (4, 5) was recorded during the HEC.

Results: Anthropometric parameters were significantly higher in the normal BMI group as compared to Low BMI group (all P<0.01). The PAL in the 2 groups was comparable. Fasting glucose levels were comparable between the groups. Basal insulin level and steady state plasma insulin values (average of 40 to 120 min) during HEC were significantly higher in normal BMI compared to low BMI group (both p<0.05). However, insulin sensitivity and glucose disposal rates during the HEC were significantly higher in the low BMI group. Heart rate, diastolic BP and systolic blood pressure increased in both the groups with hyperinsulinemia but there were no difference in the magnitude of response between the two groups (Group x Time interaction; NS). LF-RR power (nu) increased and HF-RR power (nu) decreased with hyperinsulinemia, resulting in a significant increase in LF/HF ratio but with no between group differences. The low frequency component of the SBP, increased significantly with hyperinsulinemia and there was a trend towards a reduction in baroreflex sensitivity although this was not statistically significant.

Conclusion: Cardiac sympathetic activity to hyperinsulinemia increased in both low and normal BMI groups. However, there were no between group differences. Earlier studies have suggested that insulin sensitivity is a determinant of the sympathetic response to hyperinsulinemia. The fact that the two study groups had similar autonomic responses despite differences in insulin sensitivity, suggests that there are factors other than insulin sensitivity or body composition that determine autonomic responses to hyperinsulinemia.

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C10 and PC20

A mismatched pre- and post-weaning diet has window of exposure- and sex-specific effects on energy homeostasis, adiposity and cardiovascular function in mice

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Maternal diet during pregnancy and/or lactation plays a role in inducing the offspring metabolic phenotype. We examined the phenotypic outcome in offspring if they were fed a diet mismatched between pre- and postnatal life.

Pregnant MF-1 mice were assigned to either control (C, 18% casein) or protein-restricted (PR, 9% casein) diet. PR dams were further sub-divided into those fed the PR diet throughout pregnancy (PRP) or both pregnancy and lactation (PRPL). Weaned offspring were then fed a high fat (HF, 45% Kcal fat) diet or standard chow (C, 21% Kcal fat) to adulthood. This generated six experimental groups based on dam/offspring dietary consumption: C/C, C/HF, PRP/C, PRP/HF, PRPL/C and PRPL/HF. Food intake and body weight were monitored and blood pressure was recorded by tail cuff plethysmography before animals were sacrificed. Hypothalamic tissues and fat depots were then collected for gene expression analysis by real time-PCR. Body weight and food intake was analyzed by mixed model analysis. All other data was analyzed by ANOVA with the appropriate post hoc test.

HF offspring were heavier vs. C animals, regardless of maternal diet during pregnancy. However, PRPL/HF males were lighter vs. C/HF group, but were significantly fatter ($p<0.001$). The increased adiposity observed in PRPL/HF males was not evident in the PRP/HF group. Daily energy intake was similar for all groups except for the PRP/HF males, whose intake was reduced by 20% vs. the PRP/C or C/HF groups ($p<0.001$). PRP/HF males had reduced hypothalamic mRNA levels of genes involved in appetite regulation, namely neuropeptide Y (NPY) and the leptin receptor Ob-Rb, vs. PRP/C animals ($p<0.001$ and $p<0.05$, respectively). These PRP/HF males also had reduced expression of genes involved in thermogenesis, namely beta-3 adrenergic receptor and uncoupling protein 1, in the interscapular brown adipose tissue vs. PRP/C animals ($p<0.05$). These changes in gene expression were not observed in PRPL offspring. Systolic blood pressure in all PR offspring was greater by 16% and 10% in males and females, respectively,

vs. C offspring ($p<0.05$), and increased further ($p<0.05$) by 15% and 7% in the HF male and female offspring, respectively. Our study shows that maternal protein restriction during pregnancy leads to sex-specific adaptive responses in male offspring, resulting in altered energy homeostasis following post-weaning HF-feeding. Extending maternal protein restriction to include the lactation period resulted in greater adiposity in the HF-fed male offspring. Nevertheless post-weaning HF-feeding exacerbated cardiovascular dysfunction in both male and female offspring, regardless of whether maternal protein restriction was imposed during pregnancy or both pregnancy and lactation.

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C11 and PC21

Plasma cysteine and total body fat mass in humans

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Background

Cysteine is a non-essential sulfur aminoacid, synthesized from methionine and homocysteine by the two sequential enzymes: cystathionine beta synthase (CBS) and cystathionase. Plasma total cysteine (tCys) concentrations are positively associated with body mass index (BMI) in the general population [1], but the direction of causality is unknown.

Aim

To investigate whether the association of tCys with BMI is mediated through body lean mass or fat mass, and to search the literature for underlying mechanisms.

Methods

The study included 5179 Norwegians (aged 46-73 y), recruited from the general population in the Hordaland Homocysteine Study [2], who underwent two assessments 6 y apart. Dual-energy X-ray absorptiometry was performed at follow-up. Linear regression models and concentration-response curves were used to investigate cross-sectional associations of tCys with lean mass and fat mass with adjustments for potential confounders. We also investigated associations of baseline tCys and change in tCys over 6 y with body composition at follow up

Results

tCys was not associated with lean mass, but showed a strong positive association with fat mass (partial $r=0.25$, $P<0.001$),