Oral Presentation 3

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OP 3-1 5. Diabetes and Obesity

Control of Feeding Behavior and Body Weight by Hypothalamic Cereblon (CRBN)

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Background: Cereblon (CRBN) is a substrate receptor for the CUL4A E3 ubiquitin ligase. It was discovered that CRBN KO mice show diet-induced obesity (DIO)-resistant phenotypes, including less weight gain and lower fat storage in tissues. As CRBN is known to inhibit AMPK activity, it was suggested that the resistance to DIO in CRBN KO resulted from hyperactive hepatic AMPK, which reduces lipogenic gene expressions. However, it is insufficient to explain the remarkable lean phenotypes of CRBN KO mice, and multilateral research is still required regarding CRBN's physiological actions on energy intake and expenditure.

Methods: We verified DIO-resistant phenotypes in the CRBN KO mice model and the body weight-lowering effect of CRBN inhibition by thalidomide in vivo administration. To meticulously examine the role of CRBN in body weight regulation, we established several conditional CRBN knockout mice models utilizing Cre-loxP system – e.g. KO in adipose tissue (Adiponectin-Cre;Crbn flox), nervous system (Nestin-Cre;Crbn flox), and the paraventricular nucleus of the hypothalamus (PVN) (Sim1-Cre;Crbn flox). Through AAV-mediated gene delivery, we conducted a gain-of-function study in the condition of CRBN ectopic expression in the PVN.

Results: Unlike the previous study, we consistently observed reduced food intake in high-fat diet (HFD) -fed CRBN KO mice. The administration of thalidomide, which targets the E3 ligase function of CRBN, phenocopied the bodyweight and food intake reductions in CRBN KO mice, and this bodyweight-lowering effect of thalidomide was CRBN-dependent. Moreover, as with phenotypes in CRBN whole-body KO mice, CRBN neuronal KO (NKO) mice showed decreased body weight and food intake, but neither CRBN KO nor NKO mice induced measurable alterations in energy expenditure and thermogenic gene expression in fat tissues. Thus, we hypothesized that the central regulation of food intake rather than energy expenditure is the major contributor to CRBN-mediated body weight regulation. Strikingly, while CRBN KO in the Sim1+ neurons (Sim1-Cre; Crbn flox) of the paraventricular nucleus (PVN) led to body weight and food intake reduction, AAV-mediated ectopic expression of CRBN in the PVN elicits vigorous hyperphagic obesity in mice under HFD-feeding condition.

Conclusion: We conclude that CRBN contributes to body weight control through the central regulation of feeding behavior rather than energy expenditure. Since thalidomide administration phenocopied CRBN KO, we speculate that DIO-resistance phenotypes in CRBN KO/NKO/PKO mice were led by alterations in substrate protein stability, which might act in the PVN for feeding regulation.

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Adenosylhomocysteinase-like 1 regulates nutrient-induced insulin sensitivity by interacting with IP3Rs in brown adipose tissue.

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Background: Brown adipose tissue (BAT) is essential for maintaining body temperature by burning up mitochondria in human infants and rodents during growth. Also, according to a previous paper, BAT reactivation has a therapeutic potential to combat metabolic disease. There are some reasons that calcium intake to mitochondria is related to Uncoupling protein 1 (*UCP1*) level. Adenosylhomocysteinase-like 1 (*Ahcyl1*) binds to IP3Rs and regulates calcium release. However, the role of Ahcyl1 in BAT, which is believed to regulate metabolism by calcium signaling, is not well-known.

Methods: This study presents data from BAT-specific Ahcyl1 KO mice (cKO; $Ucp1^{Cre/+}$; $Ahcyl1^{fl/fl}$) and the *Ahcyl1* KO immortalized brown preadipocyte (iBPA) cell line to evaluate highly sensitive IP3Rs-mediated thermogenesis in KO brown adipocytes and improved metabolic homeostasis.

Results: We identified that AHCYL1 acted and bound more to IP3Rs in response to calcium and adrenergic signaling while treated with the acetylcholine receptor agonist (carbachol) or norepinephrine (NE) in the iBPA cell line or wild-type mice. Also, we checked increased heat generation after acute and chronic cold stimulation with upregulated UCP1 levels in BAT of cKO mice. Consistently, KO cells revealed upregulated oxygen consumption rates. However, cKO iBAT had larger sizes of brown adipocytes than controls after chronic cold stimulation. This was because of increased lipid utilization with lipolysis and activation of nutrient-sensing kinase mTOR to supply an energy source for mitochondrial uncoupled respiration. Next, to investigate if the enhanced brown fat activation could promote insulin sensitivity, we induced insulin signaling by refeeding the standard chow diet after fasting or feeding the high-fat diet (HFD). cKO mice showed improved insulin sensitivity with upregulated p-AKT levels in epididymal white adipose tissue compared to control mice.

Conclusion: Collectively, targeting Ahcyl1 would be a potential therapeutic target for obese-induced metabolic diseases, including diabetes, by increasing energy consumption and improving insulin tolerance.

OP 3-3 1. Behavior and Public Health for Obesity

Chrononutrition behaviours and its implications to maternal gestational weight gain

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Background: Regular meal timings play an important role in maintaining healthy gestational weight gain (GWG), which is beneficial for optimum maternal and infant health. This study aims to investigate the changes of chrononutrition behaviours across trimesters and its association with GWG.

Methods: This was a prospective cohort study where 197 pregnant women were recruited at second trimester, while 138 completed follow-up data at third trimester. Chrononutrition behaviours were extracted from a self-administered 3-days food record, while GWG data was collected through antenatal health records.

Results: The mean age of the participants was 28.08 ± 3.76 years old, with the majority being Malay (72%). The average total GWG was 13.7 ± 5.7 kg, with 33% having adequate GWG, while inadequate and excessive GWG were 27% and 41% respectively. Meal timing and calorie intake remained significantly unchanged across trimesters. Prevalence of skipping breakfast for at least one day increases from second (20%) to third trimester (25%). Lunch was the largest meal throughout pregnancy with 609 (179) kcal and 607 (186) kcal in second and third trimester respectively. The average meal frequency was 4 meals, and the eating window was less than 12 hours for most pregnant women (59% vs 64%). Indulgence in night eating behaviour reduces as the pregnancy progressed (63% vs 37%). Adjusted logistic regression shows that pregnant women were more likely to have excessive GWG (AOR= 3.759, 95% CI: 1.254, 11.270; p=0.018) and inadequate GWG (Adjusted OR= 4.217, 95% CI: 1.113, 15.983; p=0.034) when frequency of breakfast skipping increases from second to third trimester.

Conclusion: Breakfast skipping habits could have a negative influence on healthy GWG of pregnant women. Future studies should determine the underlying factors of breakfast skipping habits among pregnant women to propose effective approaches to consume breakfast regularly.

OP 3-4 11. Obesity and Metabolic Syndrome in Children and Adolescents

Leptin, adiponectin, and insulin resistance in relation to hepatic steatosis in pediatric obesity

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Background: The prevalence of hepatic steatosis is increasing, and one of its risk factors is obesity. The purpose of this study is to investigate the serum biomarkers associated with hepatic steatosis in children and adolescents with obesity.

Methods: A total of 221 children and adolescents with a body mass index (BMI) above the 85th percentile (mean age: 11.01 years) were included in this study. Magnetic resonance imaging (MRI)–estimated proton density fat fraction (PDFF) was used for quantification of hepatic fat. And obesity-related hormones such as human leptin, adiponectin, and fibroblast growth factor 21 (FGF21) were measured using the participants' serum. Participants were divided into two groups based on hepatic fat fraction of 5%, group without and group with hepatic steatosis.

Results: Baseline human leptin was significantly higher and adiponectin was lower, in group with hepatic steatosis than in those without hepatic steatosis. Hepatic fat fraction was correlated negatively with adiponectin ($r = -0.25$, $p < 0.001$), and positively with human leptin ($r = 0.04$, $p < 0.001$) and homeostasis model assessment for insulin resistance (HOMA-IR; $r = 0.38$, $p < 0.001$). FGF21 showed no significant correlation with hepatic fat deposition. After adjustment for potential confounders, including BMI z-score, hepatic fat fraction was found to be independently associated with higher human leptin ($\beta = 0.20$, $p = 0.001$), and lower adiponectin ($\beta = -1.04$, $p = 0.011$).

Conclusion: The results suggest a potential role for leptin and adiponectin as non-invasive biomarkers of hepatic steatosis in children and adolescents with obesity, in which insulin resistance is likely to be involved.

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Effect of semaglutide on kidney outcomes in people with overweight or obesity and established cardiovascular disease in the SELECT trial

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Background: Obesity is an important risk factor for declining kidney function and albuminuria. Secondary analyses of cardiovascular outcome trials in people with type 2 diabetes suggest that the glucagon-like peptide-1 receptor agonist semaglutide has the potential to reduce kidney function deterioration. Semaglutide reduced the primary endpoint of major adverse cardiovascular events by 20% in the randomised controlled SELECT trial in people with overweight or obesity without diabetes. The present report is the prespecified analysis on secondary and exploratory kidney outcomes in SELECT.

Methods: The main kidney endpoint was the time from randomisation to first occurrence of a 5-component nephropathy composite comprising: death from kidney causes; initiation of chronic kidney replacement therapy (dialysis or transplantation); onset of persistent estimated glomerular filtration rate (eGFR) <15 mL/min/1.73 m^2; persistent ≥50% reduction in eGFR compared with baseline; or onset of persistent macroalbuminuria. Persistence was defined as at least two measures at least 4 weeks apart. Patients were randomised to once-weekly subcutaneous semaglutide 2.4 mg or placebo. Blood and urine samples for eGFR and urinary albumin-to-creatinine ratio (UACR) were collected at screening, at 20, 52, 104, 156, 208 weeks of follow-up and at the end of treatment. Analyses were of in-trial data and used Cox regression and mixed models for repeated measures.

Results: A total of 8803 patients were assigned to semaglutide and 8801 to placebo. The median follow-up was 182 weeks. The main composite nephropathy endpoint occurred in fewer of those assigned semaglutide (1.8% [155/8803]) than placebo (2.2% [198/8801]): hazard ratio 0.78 [95% confidence interval (CI) 0.63, 0.96]; p=0.02 (Figure 1). This effect on the main endpoint was driven by the treatment effect on onset of macroalbuminuria and, to a lesser extent, persistent ≥50% reduction in eGFR. At the prespecified 104-week time point, eGFR had declined less in the semaglutide than placebo arm, giving a treatment effect of 0.75 mL/min/1.73 m^2 [95% CI 0.43, 1.06]; p<0.001 (Figure 2A). The treatment effect on eGFR at 104 weeks was 0.57 mL/min/1.73 m2 [95% CI 0.26, 0.89] among those with eGFR ≥60 mL/min/1.73 m^2 (N=15 638) at baseline and was 2.19 mL/min/1.73 m^2 [95% CI 1.00, 3.38] in those with eGFR <60 mL/min/1.73 m2 (N=1908) at baseline. At 104 weeks the proportionate increase in UACR was less in the semaglutide than the placebo arm, with a treatment effect of −10.7% [95% CI −13.2, −8.2]; p<0.001 (Figure 2B). The treatment effect on UACR at 104 weeks was −8.1% [95% CI −10.6, −5.6], −27.2% [95% CI −35.3, −18.1] and −31.4% [95% CI −54.9, 4.3] in those with normo- (N=14 848), micro- (N=1968) and macroalbuminuria (N=325) at baseline, respectively. Semaglutide was not associated with any excess of acute kidney injury, regardless of baseline eGFR.

Conclusion: These prespecified secondary analyses suggest a beneficial effect of once-weekly subcutaneous semaglutide 2.4 mg on a composite kidney endpoint in people with overweight or obesity and established cardiovascular disease. Significant benefits for both eGFR and UACR were found, including clinically relevant lesser eGFR decline in those with baseline eGFR <60 mL/min/1.73 m^2.

Keywords: semaglutide, SELECT trial, weight loss, kidney outcome, pharmacotherapy, obesity, cardiovascular disease

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Impacts of a novel peptide, LEAP-2, administered centrally on different models of food intake in conscious rats: the gut-liver-brain interactions with acyl ghrelin

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Background: Liver-expressed antimicrobial peptide-2 (LEAP-2), an endogenous antagonist of ghrelin, inhibits ghrelin-induced food intake under freely fed state, whereas how LEAP-2 impacts on action of ghrelin under time-restricted feeding (TRF) is still unknown. This study aimed to explore central administration of LEAP-2 influencing the eating behavior evaluated by cumulative food intake under TRF state in rats.

Methods: Before intracerebroventricular (ICV) administration of O-n-octanoylated ghrelin (0.1 nmol), a food-stimulatory model, the rats were received various doses of LEAP-2 (0.3, 1, 3 nmol/rat, ICV), respectively. The cumulative food intake was recorded at 1, 2, 4, 8, 12, and 24 h immediately after ICV injection under 12-h freely fed and TRF state in light phase.

Results: Under a 12-hour freely fed state, ICV administration of ghrelin significantly stimulated food intake in rats, while pre-treatment with ICV LEAP-2 at the doses of 1 and 3 nmol inhibited the O-n-octanoylated ghrelin-induced hyperphagic effect. Under TRF state, centrally administered LEAP-2 did not reverse O-n-octanoylated ghrelin-induced food intake, which might be related to the endogenous ghrelin.

Conclusion: The centrally-administered LEAP-2 inhibits O-n-octanoylated ghrelin-induced eating behaviors under freely fed rather than TRF state. As TRF is widely applied to weight loss and improving metabolic disease, such as metabolic dysfunction-associated steatotic liver disease, the network of TRF and gut-liver hormones (ghrelin and LEAP-2) should be established in the future.