Poster Exhibition

8. Pathophysiology of Obesity and Metabolic Syndrome

PE 08-01 8. Pathophysiology of Obesity and Metabolic Syndrome

The Circadian Regulator Nobiletin Activated by ROR Inhibits Adipocyte Differentiation and Inflammation Pathway in 3T3-L1 Adipocytes

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Background: Obesity is a well-known risk factor for metabolic diseases and is often linked to chronic inflammation in fat tissue. In our previous research, we found that the natural flavonoid Nobiletin (NOB) acts as a circadian clock regulator. NOB binds directly to and activates the ROR receptors in the core circadian oscillator, significantly enhancing metabolic health in obese mice. In this study, we investigated whether the ROR receptors and the circadian oscillator play a role in the anti-obesity mechanism of NOB.

Method: 3T3-L1 preadipocyte cell lines were treated NOB (10 or 20 μM) and used for histology, RT-qPCR, Western blot, and measuring TNFα level. To monitor circadian rhythms in 3T3-L1, we generated clones with Bmal1:Luciferase reporters. To generate Rorα/γ double knockdown 3T3-L1 cell lines (Ror DKD), we performed a CRISPR system.

Results: In this study, we demonstrate that NOB enhances the oscillation of core clock genes in differentiated 3T3-L1 adipocytes, including ROR target genes. NOB also reduced lipid accumulation in 3T3-L1 cells, while disrupting the circadian expression of genes related to adipogenic differentiation, including Cebpb, Pparg, Lpl, Scd1, and Fas. Notably, 3T3-L1 Ror DKD cells significantly weakened NOB's effects on circadian gene expressions of core clock genes and adipogenic genes, and lipid accumulation. Additionally, while NOB increased the expression of IκBα, a target of RORs, to inhibit NF-κB activation and reduce proinflammatory cytokine expression, Ror DKD cells showed a stronger activation of the NF-κB pathway. This further suggests that RORs are essential for NOB's effectiveness in adipocytes.

Conclusion: These findings emphasize the important regulatory role of the NOB-ROR axis in controlling the circadian expression of clock and clock-controlled genes in 3T3-L1 adipocytes. This regulation affects adipogenic differentiation, lipid production, and inflammation.

PE 08-02 8. Pathophysiology of Obesity and Metabolic Syndrome

Genome-wide association study for metabolic syndrome reveals APOA5 SNPs with multilayered effects in Koreans

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Background: Genome-wide association studies (GWAS) investigating metabolic syndrome (MetS) have predominantly focused on non-Asian populations, with limited representation from Korean cohorts. Previous GWAS analyses have primarily emphasized the significance of top single nucleotide polymorphisms (SNPs), leaving other SNP signals poorly explained. This study aimed to reveal the interaction between rs2266788 and rs651821, the principal variants of apolipoprotein A5 (APOA5), within the most significant loci identified through GWAS for MetS. We further investigated how these variants collectively influence triglyceride and high-density lipoprotein (HDL)-cholesterol levels, both diagnostic criteria for MetS.

Methods: We conducted a comprehensive analysis using data from the Korean Genome and Epidemiology Study (KoGES) cohort, comprising 58,600 Korean individuals with available biochemical and demographic data relevant to MetS.

Results: Our findings reveal a significant association between the APOA5 SNP rs651821 and MetS and diagnostic plasma lipid levels. Notably, rs2266788 also exhibited significant associations with both triglyceride and HDL-C levels; however, a conditional analysis employing rs651821 unveiled a reversal in the odds ratio for rs2266788. Thus, rs651821 and rs2266788 emerged as independent and opposing signals in the extended GWAS analysis, namely, the multilayered effects. Further gene-environment interaction analyses regarding smoking, alcohol drinking, and physical activity underscored these multilayered effects.

Conclusion: This study unveils the intricate interplay between rs651821 and rs2266788 in MetS susceptibility. Removing the lead SNP's influence reveals an independent protective signal associated with rs2266788, suggesting a multilayered effect between the two SNPs. These findings underscore the need for novel directions in future GWAS research.

PE 08-03 8. Pathophysiology of Obesity and Metabolic Syndrome

Knowledge, Attitude and Practice Towards Cardiovascular Disease Risks Among Private University Students in Shah Alam, Selangor, Malaysia

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Background: Cardiovascular diseases (CVD) are the leading cause of death in Malaysia in 2023 with approximately 1.7 million people in Malaysia living with the three major risk factors, namely diabetes, hypertension, and high blood cholesterol. Good knowledge and attitude will help individuals to be more aware on the risk factors thus taking necessary precaution to maintain good health.

Method: A cross-sectional study involving 379 participants was conducted to determine knowledge, attitude, and practice towards CVD risk factors among students in MSU. Respondents completed an online questionnaire comprises of socio-economic and demographic section, knowledge on cardiovascular disease risks, together with attitude and practice towards prevention of cardiovascular disease.

Results: Majority of the respondents were female (58%), aged between 18 to 25 years old (87.9%), with no history of cardiovascular disease (95%). The mean score for knowledge, attitude and practice on cardiovascular disease were 0.80 ± 0.17, 4.05 ± 0.69 and 3.62 ± 0.64, respectively. There was a significant relationship between socioeconomic characteristics with knowledge on CVD risks ($p < 0.05$) but not on the attitude and practice towards prevention of CVD ($p > 0.05$).

Conclusion: This study revealed that respondents had moderate knowledge and good attitude/practice towards prevention of CVD. A health promotion campaign at the university setting could create awareness on cardiovascular disease risks and ensure necessary precaution can be implemented to reduce the risks thus protecting cardiovascular health of individuals.

Keywords: Cardiovascular disease, knowledge, attitude, practice, risk factors

PE 08-04 8. Pathophysiology of Obesity and Metabolic Syndrome

Long-term high-fructose high-fat diet renders the retina more susceptible to blue light in mice via AGE/RAGE-induced inflammasome activation

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Background: Blue light (BL) has short wavelengths and higher energy, enabling it to penetrate the eyeball and cause retinal photochemical damage by excessive generation of reactive oxygen species. Given the lack of studies about the influence of dietary factors on the susceptibility to BL phototoxicity, this study aimed to investigate the impact of a long-term high-fructose and high-fat (HFHF) diet on the development of retinal damage by BL exposure.

Methods: A total of 24 male ICR mice were randomly assigned to three groups: control, BL exposure (BL), and BL exposure plus HFHF diet (BL + HFHF) groups. Following a duration of 40 weeks adhering to the HFHF diet, the mice were exposed to low-intensity BL for eight weeks, with a cumulative exposure time of 6 h per day.

Results: The results showed that the HFHF diet led to visceral fat accumulation, elevated levels of blood total cholesterol, protein carbonyl group, and fluorescent advanced glycated end products (AGEs) in mice. Immunofluorescence staining (IF) showed that BL caused the loss of rhodopsin, activation of Müller glial cells, and a significant elevation in the oxidative stress marker 8-hydroxy-2-deoxyguanosine ($p < 0.05$) as compared to the control group. The HFHF diet had a significant impact on the adverse outcomes of BL, resulting in increased permeability of the blood-retinal barrier and elevated levels of the pro-inflammatory IL-1β and TNF-α, along with the apoptosis-related caspase-3 and inflammasome NLRP3 and caspase-1 proteins ($p < 0.05$). In the HFHF diet group, the deposition of Nε-(1-carboxyethyl)-L-lysine and Nδ-(5-methyl-4-imidazolon-2-yl)-L-ornithine was observed in retinal tissues together with the activation of the receptor for AGE.

Conclusion: This study proposes that the inflammasome activation triggered by the AGE/RAGE pathway in response to an HFHF diet could potentially worsen BL toxicity and that unhealthy dietary patterns may have detrimental effects on visual health.

Keywords: AGEs, blue light, high-fructose and high-fat diet, oxidative stress, retina

PE 08-05 8. Pathophysiology of Obesity and Metabolic Syndrome

Metabolic and Mitochondrial Pathways Influenced by Estrogen and Testosterone in Transgender Individuals: A Metabolomic and Machine Learning Approach

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Background: Mitochondria are crucial for energy in skeletal muscle. The impact of hormone therapy on mitochondrial function in transgender individuals is not well understood. This study investigates how estrogen and testosterone affect mitochondrial bioenergetics and identifies distinct metabolic signatures. We also explore implications for managing obesity and MetS in transgender people.

Method: We analyzed data from the NIH Common Fund Metabolomics Program and the UK Biobank, focusing on 300 transgender participants (150 on estrogen, 150 on testosterone therapy). High-resolution metabolomic data, including over 1,000 metabolites, were examined to assess bioenergetic pathways like the TCA cycle and fatty acid oxidation. Mitochondrial function metrics, such as density and ATP production, were derived. Clinical metrics included BMI, fasting glucose, lipid profiles, hormone regimens, and serum hormone levels. We used Principal Component Analysis (PCA) and Random Forest for feature ranking, and predictive modeling with Support Vector Machines (SVMs) and Neural Networks to identify metabolomic signatures linked to MetS outcomes, evaluated by AUC, precision, recall, and F1-score.

Results: Estrogen therapy increased mitochondrial density by 20% and ATP production by 15% ($p<0.01$). Testosterone therapy decreased mitochondrial density by 10% and ATP by 12% ($p<0.05$). Estrogen boosted TCA cycle metabolites (1.5x-1.7x, $p<0.01$) and reduced fatty acid oxidation markers (0.6x, $p<0.05$). Testosterone increased branched-chain amino acids (1.4x, $p<0.05$) and oxidative stress markers (1.3x, $p<0.05$). Our SVM model accurately predicted MetS (AUC 0.92, precision-recall AUC 0.89), emphasizing TCA cycle intermediates and mitochondrial respiration as key predictors. Estrogen upregulated oxidative phosphorylation and glycolysis (scores 2.3 and 1.9, $p<0.01$), while testosterone enhanced amino acid metabolism and ROS detoxification (scores 1.8 and 2.0, $p<0.01$).

Conclusion: Estrogen therapy improves mitochondrial function, while testosterone reduces it in transgender individuals. Metabolomic analysis reveals unique pathways influenced by each hormone. Improved mitochondrial health is key for managing obesity and MetS, emphasizing the potential for targeted interventions.

PE 08-06 8. Pathophysiology of Obesity and Metabolic Syndrome

Hepatocyte-derived extracellular vesicles mediate endothelial dysfunction in metabolic dysfunction-associated steatotic liver disease

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is an independent risk factor for cardiovascular disease (CVD), although the mechanism of association is still unclear. Extracellular vesicle (EV) is a biological nanoparticle that plays critical roles in intercellular crosstalk. We aimed to investigate the effect of hepatocyte-derived EVs on endothelial cells in MASLD condition.

Methods: Hepatocytes isolated from C57BL6 mice were exposed to palmitic acid (PA). Mice were fed a Gubra-Amylin Nonalcoholic steatohepatitis (GAN) diet for MASLD model. Human umbilical vein endothelial cells (HUVEC) and human aortic endothelial cells (HAEC) were treated with EVs released from hepatocytes.

Results: The amount of EVs derived from PA-treated hepatocytes was greater than the EVs from control hepatocytes. Fluorescence-labeled hepatic EVs uptake were detected in endothelial cells. Treatment of EVs derived from PA-exposed hepatocytes induced endothelial dysfunction with subsequent upregulation of inflammatory cytokines, adhesion molecules, and oxidative stress markers in HUVEC/HAEC. Small RNA profiling of miRNA isolated from PA-treated hepatic EVs identified 23 upregulated and 4 downregulated miRNAs. miR-30b-5p was identified as a possible candidate cargo and its elevation was confirmed by qPCR in EVs from PA-treated hepatocytes and GAN diet-induced fatty liver. We identified Elovl5 as a direct target of miR-30b-5p, a key enzyme in fatty acid elongation. Overexpression of miR-30b-5p inhibited the elongation of polyunsaturated fatty acids (PUFA), and similar results were observed when the expression of Elovl5 was knocked down by Elovl5 siRNA. Suppression of Elovl5 resulted in endothelial dysfunction which was rescued by supplementation of PUFAs.

Conclusion: Our findings suggest a novel role of hepatic EVs that regulate crosstalk between hepatocytes and endothelial cells. This may explain the independent relationship between MASLD and CVD.

PE 08-07 8. Pathophysiology of Obesity and Metabolic Syndrome

Aged-induced nonalcoholic fatty liver disease seems to inversely correlated with iron and vitamin D

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Background: Nonalcholic fatty liver disease (NAFLD) is the most common chronic liver disease, linked to obesity and diabetes. Excess iron worsens NAFLD by disrupting lipid metabolism via reactive oxygen species and mitochondrial dysfunction. Herein, we found that iron was excessively accumulated in the liver of aged mice, and discovered that vitamin D alleviates this iron overload.

Method: 3- or 18-month-old mice were divided into two groups and fed a standard chow diet containing vitamin D3 (1000 IU/kg) or a standard chow diet enriched with vitamin D3 (20,000 IU/kg) for 4 months (n = 10-12 per group).

Results: Aging is a well-known risk factor for NAFLD. Previously, we demonstrated that vitamin D3 prevents age-induced NAFLD by increasing the level of mitochondrial cristae organizing system (MICOS) 60. To further investigate the precise mechanisms underlying age-induced liver changes, we conducted a differential gene expression (DEG) analysis with vitamin D3-treated aged livers compared to young and old chow diet-fed mice. Our findings indicate significant inverse changes in metabolic pathways involved in lipid and cholesterol regulation in vitamin D3-treated aged livers compared to controls. Additionally, total OXPHOS proteins were significantly increased in vitamin D3-treated aged livers compared to those from aged livers on a chow diet.
Twenty-two-month-old C57BL6 mice displayed hepatic steatosis, hepatomegaly, elevated blood triglycerides, and free fatty acids. Concomitantly, we observed liver iron accumulation in aged mice by immunostaining using ferritin heavy chain antibodies. Aged livers exhibited increased ferritin-positive cells per area, whereas vitamin D3-treated aged mice showed a reduction of iron accumulation. Notably, vitamin D3 did not affect ferritin heavy chain protein or RNA levels, but it did regulate ferritin light chain transcript levels.

Conclusion: Sufficient intake of vitamin D is expected to play a very effective role in preventing non-alcoholic fatty liver disease (NAFLD). Vitamin D3 may influence hepatic steatosis by modulating metabolic genes and iron accumulation in aging livers.

PE 08-08 8. Pathophysiology of Obesity and Metabolic Syndrome

Serotonin 2C Receptors Expressed by TRH Neurons Regulate Metabolism

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Background: The thyrotropin-releasing hormone (TRH) neurons are neurohormone-expressing neurons that regulate metabolism. Since it was previously shown that TRH neurons express serotonin 2C receptor (Htr2c) that controls many aspects of metabolism, we aimed to identify the metabolic role of Htr2c expressed by TRH neurons.

Methods: We performed experiments to characterize metabolic phenotypes with Trh-ires-cre::Htr2cflox/Y and Htr2cflox/Y mice fed high fat diet. We measured body weight, food intake, energy expenditure, and performed glucose tolerance test and insulin tolerance test. We also recorded the electrical activity of TRH neurons using patch-clamp technique from the Trh-ires-cre::tdTomato reporter mice.

Results: We did not observe any significant difference in body weight, food intake, and energy expenditure, insulin tolerance test between the Trh-ires-cre::Htr2c$^{flox/Y}$ and Htr2c$^{flox/Y}$ mice. However, fasting glucose level was significantly lower in Trh-ires-cre::Htr2c$^{flox/Y}$ mice compared to Htr2c$^{flox/Y}$ mice. In addition, Trh-ires-cre::Htr2c$^{flox/Y}$ mice showed improved glucose tolerance compared to Htr2c$^{flox/Y}$ mice. We also found that CP809101, an Htr2c agonist, does not affect TRH neurons within the paraventricular nucleus of the hypothalamus (PVH), but inhibits TRH neurons within the dorsomedial nucleus of the hypothalamus (DMH).

Conclusion: We found that Htr2c expressed by TRH neurons regulate fasting glucose levels without affecting body weight, food intake, and energy expenditure. We also provide evidence that the observed phenotypes may not be due to the activity of PVH TRH neurons, but Htr2c may work on DMH TRH neurons to regulate glucose homeostasis. Our findings provide insight how Htr2c expressed by TRH neurons regulate metabolism.

PE 08-09 8. Pathophysiology of Obesity and Metabolic Syndrome

Role of dorsal raphe serotonergic neurons in sodium appetite

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Background: An animal with sodium deficiency develops sodium appetite which drives it to consume more
sodium. Although a lot of studies have been performed to understand how sodium depletion may lead to the development of sodium appetite, current understanding on the mechanisms is incomplete. In particular, while the relationship between serotonin receptors and sodium appetite has been suggested for a long time, it is still unclear how serotonin controls sodium appetite in response to sodium depletion. Hence, we targeted serotonergic neurons in the dorsal raphe nucleus (DRN) in brainstem, which releases more than 50% of serotonin in the brain.

Method: We performed immunohistochemistry and patch-clamp experiments to examine the activity DRN serotonergic neurons in several conditions. Blood pressure was measured by a non-invasive system. For some experiments, drugs were given via an intracerebroventricular cannula or a subcutaneous minipump.

Results: We found that DRN serotonergic neurons were activated by sodium depletion. Drug-induced hypotension had only minimal effects on the activity of serotonergic neurons and no effects on sodium appetite. Notably, angiotensin II (ATII) was sufficient to activate DRN serotonergic neurons and increase sodium appetite in euvolemia. We also found evidence that ATII receptors are necessary to activate DRN serotonergic neurons and induce sodium appetite in sodium depletion.

Conclusion: In this study, we found that DRN serotonergic neurons are activated in response to sodium depletion. We also found that it is not decreased blood pressure but ATII, which was released presumably in response to volume depletion, that activates DRN serotonergic neurons.

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Metabolic Function of Leucine-Rich Repeat Transmembrane Neuronal 4 Expressed by Arcuate AgRP Neurons

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Background: It is well known that the agouti-related peptide (AgRP)-expressing neurons of the arcuate nucleus of the hypothalamus regulate energy balance and glucose homeostasis. While it was previously shown that excitatory and inhibitory synaptic input onto the AgRP neurons influence the activity and metabolic function of AgRP neurons, little is known about the role of synaptic adhesion molecules therein. In this study, we focused on a synaptic adhesion molecule, leucine-rich repeat transmembrane neuronal 4 (LRRTM4), which is expressed by post-synaptic part of excitatory synapses to be involved in synapse formation and synaptic transmission.

Methods: We generated conditional knockout mice which lacks LRRTM4 specifically in the AgRP neurons ($AgRP^{LRRTM4\text{-}KO}$ mice). We measured body weight, food intake, and energy metabolism, and tested glucose homeostasis to see physiological functions of LRRTM4 in AgRP neurons. We also measured electrophysiological properties of $AgRP^{LRRTM4\text{-}KO}$ neurons.

Results: We confirmed successful deletion of ^{LRRTM4} in the AgRP neurons and found that excitatory postsynaptic current is significantly decreased in $AgRP^{LRRTM4\text{-}KO}$ neurons. We found that AgRPLRRTM4-KO mice show improved insulin sensitivity but normal food intake, body weight, and energy metabolism phenotypes.

Conclusion: Our results provide insight how synaptic machinery of hypothalamic AgRP neurons can shape in vivo metabolic function.

PE 08-11 8. Pathophysiology of Obesity and Metabolic Syndrome

Food insecurity during developmental period promotes addictive-like eating by reshaping top-down circuitry

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Background: Food insecurity is condition of limited or uncertain access to adequate food.. It is linked to binge eating, obesity, depression, cognitive and behavioral problems, and mental health issues in adolescents and adults. However, the neural mechanism of the effect of developmental feeding history is unknown.

Method: We developed food insecurity disease model development protocol. Furthermore, we investigated if the disease phenotypes persisted after the mice were provided with sufficient food (recovery study). Mice were weaned at P21 and stereotactic surgery for longitudinal recording at P28. The mice were assigned to either the food secure group (FS) or the food insecure group (FI) for the food paradigm. FS mice were given food only during the dark cycle of each day, while FI mice were randomly given food only during the dark cycle. Longitudinal recordings were used by photometry to monitor neural signal changes in response to the food by schedule. Addictive-like eating behaviors are measured by progressive ratio, binge eating tests, and social versus food experiments.

Results: Food insecurity group (FI) showed increased dopamine release for food as the disease development protocol progressed. The breakpoint of PR and food intake of binge-eating test was increased, which indicate that food insecurity experience could increase motivation for food and addictive eating behaviors. In addition, during the recovery period after the food paradigm, the fat composition and body weight in the FI group were significantly higher than in the FS group.

Conclusion: Our findings suggest that food insecurity leads to increased dopamine release and reinforces motivation for food, contributing to addictive-like eating behaviors in mice. This indicates that developmental feeding history significantly impacts neural mechanisms underlying eating behavior.

PE 08-12 8. Pathophysiology of Obesity and Metabolic Syndrome

The Role of Glucagon-like Peptide 1 Receptor (GLP-1R) Neuron in Central Amygdala on Aversion and Nausea

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Background: Glucagon-like peptide 1 (GLP-1) and its receptor GLP-1R play a crucial role in regulating satiety and food intake. Although their outstanding therapeutic properties, the mechanism of central GLP-1 signaling, including its functions and side-effects, remains poorly known. Here, we aim to test the role of GLP-1R expressing neurons in the central amygdala (CeA), a major emotion center, and their downstream projection.

Methods: We used optogenetics to determine how $CeA^{Glp\text{-}1r}$ neurons influence feeding behavior, and calcium imaging to investigate their natural activity. Finally, we used virus neuronal tracing to discover the inputs and outputs of $CeA^{Glp\text{-}1r}$ neurons.

Results: Using optogenetics, we demonstrated that the activation of $CeA^{Glp\text{-}1r}$ neurons abolishes food intake in fasted mice. Also, the activation of $CeA^{Glp\text{-}1r}$ neurons also attenuated the voracious feeding of the binge-eating disease model (BEM). $CeA^{Glp\text{-}1r}$ neurons encode negative-valence, which leads to food aversion. Using calcium imaging, the neuronal activity of $CeA^{Glp\text{-}1r}$ increases not only to positive stimuli like food, and but also to negative stimuli, including visceral malaise, bitter liquid, and shock. Finally, $CeA^{Glp\text{-}1r}$ neurons project to lateral habenula (LHb), subthalamic nucleus (STN), substantia nigra (SNR), and anterior thalamus (AT).

Conclusion: In summary, these experiments reveal a novel role of GLP-1R in central amygdala on food aversion. Our findings suggest that pharmaceutical targeting, with the exception of $CeA^{Glp\text{-}1r}$ signaling, will improve efficacy in treating obesity and diabetes by reducing nausea and anxiety.

PE 08-13 8. Pathophysiology of Obesity and Metabolic Syndrome

Regulation of odor induced appetite by SST Neurons in the Olfactory Tubercle

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Background: At some point, we've all been overtaken by an intense craving for chicken after smelling it. Just like this, olfactory stimuli have a significant impact on food consumption motivation, yet research on this remains limited. The Olfactory Tubercle(OT) is well-known to directly receive olfactory information from the olfactory bulb, piriform cortex and receive dopamine from the Ventral tegmental area and somatostatin(SST) neurons play a key role in olfaction.

Method: To measure neural activity, we used GCaMP virus and Fiber photometry.
To modulate neural activity, we used ChR2 and NpHR viruses with 473nm and 532nm laser respectively.

Results: We discovered that the OT^{SST} neurons were activated by olfactory food information to a higher degree than visual food information. And the response to the same olfactory cues significantly increased after learning they were associated with food. Activation of OT^{SST} neurons induced a strong motivation for food consumption and increased food intake even in the presence of bitter taste. Inhibition of OT^{SST} neurons reduced food intake and increased access to food.
These data indicate that OT^{SST} neurons receives information from the olfactory system and responds specifically to food odors, playing a crucial role in food intake.

Conclusion: In conclusion, the OT^{SST} neurons play a crucial role in regulating food intake by responding more strongly to olfactory cues than visual cues, thereby significantly increasing motivation and consumption behaviors related to food.

PE 08-14 8. Pathophysiology of Obesity and Metabolic Syndrome

Neural Mechanisms for Atypical Antipsychotics-induced Hyperphagia and Obesity

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Background: Atypical antipsychotics (AAPs), such as risperidone and olanzapine, are widely prescribed for neuropsychiatric disorders like schizophrenia and bipolar disorder. Despite their therapeutic efficacy, AAPs are associated with metabolic side effects, including severe weight gain and obesity. Given the previously reported downregulation of melanocortin-4 receptor (MC4R) by AAPs, this study aimed to investigate the cellular signaling pathway of the inhibitory effect of AAPs on MC4R-expressing neurons within the paraventricular nucleus of the hypothalamus (PVH) ($MC4R^{PVH}$ neurons). Additionally, we examined in vivo effects of an AAPs-containing diet on $MC4R^{PVH}$ neurons.

Methods: We conducted whole-cell patch-clamp recordings on *Mc4r-cre::Ai14* mice to investigate the acute effects of risperidone on $MC4R^{PVH}$ neurons. Subsequently, cell-attached patch-clamp and whole-cell voltage-clamp recordings were performed on *Mc4r-cre:Ai14* mice fed a risperidone diet. For comparative analysis, the same experiments were conducted with olanzapine.

Results: We found that treatments with risperidone inhibited $MC4R^{PVH}$ neurons via a cAMP/PKA-dependent activation of a K_{ATP} channel in both male and female mice. Notably, the *in vivo* effect of risperidone showed sexual heterogeneity; the activity of $MC4R^{PVH}$ neurons was decreased only in female mice fed a risperidone diet. In contrast, while acute application of olanzapine inhibited $MC4R^{PVH}$ neurons in a similar manner to risperidone, consumption of olanzapine diet did not significantly alter the activity of MC4RPVH neurons in both male and female mice.

Conclusion: In In this study, we delineated the cellular mechanisms underlying the inhibition of $MC4R^{PVH}$ neurons by AAPs. It is notable that a risperidone diet inhibits $MC4R^{PVH}$ neurons only in female mice, which coincides with the more prominent hyperphagia and obesity effects observed in women. The hypothalamic mechanisms underlying olanzapine-induced hyperphagia require further investigation. This study enhances our understanding of the metabolic syndromes associated with AAPs and supports the development of targeted therapeutic interventions to mitigate adverse outcomes of AAPs use.

PE 08-15 8. Pathophysiology of Obesity and Metabolic Syndrome

Visceral Adipose Dendritic Cells Modulate Obesity-induced Regulatory T Cell Development through IL-33

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Background: Regulatory T cells (Tregs) residing in visceral adipose tissue (VAT) play a pivotal role in regulating tissue inflammation and metabolic dysfunction associated with obesity. However, the specific phenotypic and functional characteristics of Tregs in obese VAT, as well as the regulatory mechanisms shaping them, remain elusive.

Method: Diet-induced obesity was induced in C57BL/6J mice using a high-fat diet. In vivo characterization of Tregs and antigen presenting cells (APCs) in ATs was performed using flow cytometry. In vitro co-culture experiments for Treg differentiation were conducted by seeding sorted primary APCs isolated from ATs of lean and obese mice with naïve CD4+ T cells for 5 days.

Results: This study demonstrates that obesity selectively reduces Tregs in VAT, characterized by restrained proliferation, heightened PD-1 expression, and diminished ST2 expression. Additionally, obese VAT displays distinctive maturation of dendritic cells (DCs), marked by elevated expressions of MHC-II, CD86, and PD-L1, which are inversely correlated with VAT Tregs. In an in vitro co-culture experiment, only obese VAT DCs, not macrophages or DCs from subcutaneous adipose tissue (SAT) and spleen, result in decreased Treg differentiation and proliferation. Furthermore, Tregs differentiated by obese VAT DCs exhibit distinct characteristics resembling those of Tregs in obese VAT, such as reduced ST2 and IL-10 expression. Mechanistically, obesity lowers IL-33 production in VAT DCs, contributing to the diminished Treg differentiation.

Conclusion: These findings collectively underscore the critical role of VAT DCs in modulating Treg generation and shaping Treg phenotype and function during obesity, potentially contributing to the regulation of VAT Treg populations.

Keywords: obesity, inflammation, adipose tissue dendritic cell (ATDC), regulatory T cell (Treg), adipose tissue macrophage (ATM)

PE 08-16 8. Pathophysiology of Obesity and Metabolic Syndrome

Activation of OlfrX by Induces Thermogenesis in Brown Adipose Tissues

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Background: Olfactory receptors are widely expressed in extra-nasal tissues, where they regulate cell type-specific signal transduction pathways. This study investigated biological functions of Olfactory receptor X (OlfrX) in brown adipose tissue (BAT).

Methods: C3H10T1/2 cell and primary adipocytes from 6-7 male C57BL/6N mice and OlfrX-/- were used to examine biological functions of OlfrX in vitro. OlfrX gene was silenced with siRNA. For in vivo analysis, mice were first orally administered with ligand N (at a dose of 10 mg/kg body weight, dissolved in methyl cellulose), or distilled water (used as the vehicle) daily for 2 weeks. Following the two-week oral administration of ligand N, mice were exposed to acute cold conditions (4°C) for 6 hours. Protein and mRNA expressions were analyzed by Western blotting and quantitative PCR, respectively.

Results: OlfrX expression is confirmed by qPCR and immunoblotting assays in cultured brown adipocytes. Immunocytochemistry showed that OlfrX protein is expressed in plasma membrane as well as cytosol. Treatment of an OlfrX ligand induced thermogenic gene expressions of Ucp1 and Pgc1α in cultured brown adipocytes but the inductions were abrogated when OlfrX gene was silenced with siRNA. OlfrX did not influence the levels of second messengers such as cAMP, intracellular calcium, and inositol phosphates, however, OlfrX activated the noncanonical β-arrestin-ERK1/2 signaling pathway. Thus, treatment of barbadin, ß-arrestin inhibitor, negated the induced ERK1/2 phosphorylation by OlfrX activation. Mice exposed to an acute cold exposure (4 , 6 hrs) led to higher rectal and surface body temperatures, while these effects were abolished in Olfr558 deficient mice. Ligand activation of OlfrX induced UCP1 and PGC-1α expression in BAT of wildtype mice but not in OlfrX deficient mice. OlfrX did not affect the expression of genes involved in UCP1-independent futile cycles.

Conclusion: OlfrX may regulate non-shivering thermogenesis by inducing UCP1 and PGC-1α expression through the β-arrestin-ERK1/2 signaling pathway.

PE 08-17 8. Pathophysiology of Obesity and Metabolic Syndrome

Regulation of Senescence Signaling by Filbertone in Skeletal Muscle Cells

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Background: Muscle aging and obesity are interconnected health issues that significantly impact the quality of life, especially in older adults. As muscle mass and strength decline with age, a condition known as sarcopenia, individuals often experience reduced mobility and an increased risk of falls. Concurrently, obesity exacerbates these problems by adding excess weight, which places additional strain on weakened muscles and joints. The combination of sarcopenia and obesity, sometimes referred to as sarcopenic obesity, leads to a vicious cycle of decreased physical activity and further muscle deterioration. It has been demonstrated that Filbertone, the main flavor compound in hazelnuts, has been shown to prevent hypothalamic inflammation, obesity, neurodegenerative diseases, and muscle lipid accumulation. However, its effect on muscle aging has not been explored.

Method: This study aimed to investigate the impact of filbertone on muscle aging in C2C12 myotubes induced to senescence by doxorubicin or H2O2. To understand the mechanisms behind filbertone's effects, we performed experiments including western blot analysis, reverse transcription quantitative polymerase chain reaction (qRT-PCR), and senescence-associated β-galactosidase (SA-β-gal) staining.

Results: Filbertone was found to reduce the protein levels of p53 in senescent skeletal muscle cells without affecting the mRNA levels. Additionally, the expression of muscle-related genes such as myogenin and muscle RING-finger protein-1 (MuRF1) was significantly increased in senescent muscle cells treated with filbertone. Moreover, the number of senescent skeletal muscle cells showing β-galactosidase activity was significantly decreased with filbertone treatment.

Conclusion: These findings indicate that filbertone is essential in regulating muscle aging and could be instrumental in developing better strategies for the prevention and treatment of muscle aging.

PE 08-18 8. Pathophysiology of Obesity and Metabolic Syndrome

Long-term Exercise-mediated Changes in Inflammatory Marker and Adipocytokines in Middle Aged Women by UCP2 Gene Polymorphism

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Background: Physical exercise is assumed to benefit the regulation of inflammatory markers and enhance the anti-inflammatory index. This study aimed to compare the markers of metabolic syndrome and the levels of adipocytokines according to the UCP2 gene types at baseline and assess whether genetic variations of UCP2 may affect exercise-mediated changes in metabolic syndrome markers and adipocytokines.

Methods: Forty-two sedentary healthy middle-aged women (52.74±6.39 years old) participated in this study. Participants were encouraged to train thrice a week for six months, 60 minutes per treadmill walking / running session at 60% VO2R. Genotypes were identified as homozygous in the 3'-UTR of exon-8 (DD), heterozygous (DI), and homozygous in 3'-UTR of exon-8 (II). DD and DI genotypes of the UCP-2 gene were seen in 23(57.1%) and 19(42.9%) subjects, respectively.

Results: The DD genotype body weight, BMI, % body fat, and waist circumstance significantly decreased whereas body weight, BMI, and waist circumference in the ID genotype significantly decreased after the six-month exercise program. There were no significant changes of metabolic markers in ID genotypes whereas insulin and HOMA-IR in DD genotype were significantly decreased after the exercise program. In the DD genotype, after 6 months of aerobic training adiponectin was significantly increased and leptin, TNF-α, and IL-6 were significantly decreased. In the ID genotype, TNF-α was significantly decreased after exercise training.

Conclusion: The beneficial actions of physical exercise to suppress the production of inflammatory markers such as TNF-α and enhance the anti-inflammatory index such as adiponectin may depend on the genotype of UCP2.

PE 08-19 8. Pathophysiology of Obesity and Metabolic Syndrome

Zona Incerta GABAergic Circuits Integrated Consummatory Behaviors under Motivational Conflict

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Background: Zona incerta(ZI) is known to regulate survival behaviors such as flight, drinking and food intake. Despite its various functions and extensive connections with many brain regions, the organizational and functional dynamics of ZI GABAergic circuits across different behaviors, and how these circuits contribute to specific behavioral phases are poorly understood.

Method: Using genetic, optical recording and manipulation tools, we monitored activity of ZI GABAergic neurons to specific rewards and their subsequent behavioral outcomes.

Results: We observed that ZI GABAergic neurons are activated at the onset of biting food, responding to various reward consummatory behaviors. This neural activity specific to certain rewards is disrupted when other motivations are present by need deprivations. Through optogenetic activation, we demonstrated that stimulating ZI GABAergic neurons promoted biting behavior, even towards non-food objects and bitter food. It induced abnormal persistent biting behavior such as biting the water dish despite dehydration and biting the shock-delivering rod, overriding natural responses.

Conclusion: Our findings highlight the complex and critical role of ZI GABAergic neurons in behavior regulation, providing insights into how specific neuronal activities shape decision-making processes under competitive motivational states. This study provides compelling evidence that ZI GABAergic neurons integrate and arbitrate motivational conflicts, influencing consummatory behaviors.

PE 08-20 8. Pathophysiology of Obesity and Metabolic Syndrome

Exploring Network Pharmacology and Molecular Docking of E.tapos Yoghurt to Combat Maternal Obesity

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Background: Maternal obesity, characterized by an elevated body mass index (BMI) during pregnancy, is known to have adverse effects on the offspring. However, a recent study suggests that Elateriospermum tapos (E. tapos) yoghurt may hold potential in mitigating excessive weight retention post-pregnancy. Thus, this study aims to employ network pharmacology to explore the pharmacological effects of the bioactive compounds present in E. tapos yoghurt against maternal obesity.

Methods: Initially, a screening process is conducted to identify the bioactive compounds in E. tapos yoghurt, followed by the prediction of potential gene targets for these compounds using Swiss Target Prediction and SuperPred databases. Maternal obesity-associated genes are sourced from the OMIM, DisGeNet, and GeneCards databases. The interaction between the identified compounds and maternal obesity genes is established through protein-protein interaction analysis, gene ontology examination, and KEGG pathway analysis. To validate the results, molecular docking studies are conducted using AutoDock Tools software.

Results: The findings reveal that out of the 64 compounds analyzed, three meet the screening criteria, resulting in a total of 380 potential gene targets. Among these targets, 240 are shared with maternal obesity-related genes. Further analysis demonstrates the favorable affinity of these active compounds with key targets, linking them to biological processes involving protein phosphorylation, inflammation, as well as pathways related to lipid metabolism, atherosclerosis, and other signaling pathways.

Conclusion: In conclusion, this study provides valuable insights into the potential pharmacological effects of the bioactive compounds found in E. tapos yoghurt against maternal obesity. These findings open avenues for further exploration and potential therapeutic interventions targeting maternal obesity.

PE 08-21 8. Pathophysiology of Obesity and Metabolic Syndrome

CELLULAR QUISENCENCE IMPAIRS ADIPOCYTE PROGENITOR CELLS DIFFRENTITATION; LEADING TO HYPERTROPHIC EXPANSION OF VISCERAL ADIPOSE TISSUE IN OBESE INDIVIDUALS

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Background: Visceral adipose tissue expansion along with adipocyte hypertrophy are negative determinants of obesity related metabolic diseases such as type 2 diabetes mellitus, hypertension, dyslipidemia and atherosclerosis. Pre-adipocytes exist in a state of cellular quiescence which affects their ability to differentiate into mature adipocytes in response to caloric excess leading to a hypertrophic expansion of adipose tissue. Understanding the genes controlling; pre-adipocyte cellular dormancy will aid us to better tackle adipose tissue dysfunction in obesity and dampen the metabolic complications associated with it.

Method: Obese subjects aged 18-60 years undergoing bariatric surgery (BMI ≥ 35; n=12) and their age matched controls (BMI, non-diabetic < 25; n=10) were recruited. Visceral adipose tissue was digested and separated into stromal vascular cells and mature adipocytes based on buoyancy. The size of mature adipocytes was measured using microscopy. The pre-adipocytes were isolated from stromal vascular fraction using FACS; RNA extracted and m-RNA sequenced. Reads were aligned using HISAT-2 and fold change calculated. Results were analyzed statistically by Student's t-test, and correlation analysis with anthropometric measurement.

Results: Percentage of preadipocytes was inversely correlated with BMI (p-value – 0.04) but no significance difference was observed between obese and non-obese (p - 0.1). Mean diameter of mature adipocytes was significantly higher in obese compared to non-obese (p – 0.04). From the differentially expressed genes (DEGs) two were mapped to "cellular quiescence" by Gene Ontology analysis. NR4A1 and TEAD4 were raised in obese with a (log-FC – 2.88 and 2.36) and (p – 0.01 and 0.005).

Conclusion: Though percentage of pre-adipocyte cells are not significantly reduced in obese individuals; due to upregulation of quiescent genes there is reduced visceral adipose tissue hyperplasia and increased hypertrophy leading to metabolic disturbances as seen in obesity.

PE 08-22 8. Pathophysiology of Obesity and Metabolic Syndrome

CD2 biased immune response skews the SAG mediated therapy for a predominant Th1 response in experimental visceral leishmaniasis infection in light of obesity

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Background: Visceral leishmaniasis is a macrophage associated disorder which leads to a profound decrease in the natural immunotherapeutic potential of the infected subjects to combat the disease. Visceral leishmaniasis is a macrophage associated disorder which leads to a profound decrease in the natural immunotherapeutic potential of the infected subjects to combat the disease. We have evaluated the effect of combining CD2 with conventional antimonial (sb) therapy in protection in BALB/c mice infected with either drug sensitive or resistant strain of Leishmania donovani with 3×10(7) parasites via-intra-cardiac route. Obesity is the main causal factor for metabolic syndrome and chronic systemic inflammation, which impacts on immune function and increases susceptibility to pathogens. Several reports suggest that obesity can interfere with responses to pathogen-derived signals and impair the development of protective anti-Leishmania immunity.

Methods: Mice were treated with anti CD2 adjunct SAG sub-cutaneously twice a week for 4 weeks. Assessment for measurement of weight, spleen size, anti-Leishmania antibody titer, T cell and anti-leishmanial macrophage function was carried out day 0, 10, 22 and 34 post treatments.

Results: The combination therapy was shown boosting significant proportion of T cells to express CD25 compared to SAG monotherapy. Although, the level of IFN-γ was not statistically different between combination vs monotherapy (p=0.298) but CD2 treatment even alone significantly influenced IFN-γ production than either SAG treatment (p=0.045) or with CD2 adjunct SAG treatment (p=0.005) in Ld-S strain as well as in Ld-R strain. The influence of CD2 adjunct treatment was also documented in anti-leishmanial functions in macrophages.

Conclusion: Drug resistance is the major impedance for disease control but the encouraging results obtained after infecting mice with resistant strain of the parasite strongly imply that this drug can be effective even in treating resistant cases of Kala-azar. Also diet can also play a major role in the effective recovery of the disease.

PE 08-23 8. Pathophysiology of Obesity and Metabolic Syndrome

Serum Leptin level in women with Polycystic ovarian syndrome and its correlation with Insulin resistance.

huda naaz

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Introduction: Polycystic ovarian syndrome is a common endocrinological disorder, among women of reproductive age with global prevalence up to 5- 7 %, which is frequently associated with chronic anovulation, hyperandrogenimia, insulin resistance and obesity. Leptin, hormone product of obesity (ob) gene, synthesized exclusively in adipose tissue. Recently Leptin resistance has been reported to have key role in development of obesity also accompanied by insulin resistance(IR), compensatory hyperinsulinemia suggesting the possibility of interaction between insulin and leptin. However, the relationship between Leptin and Insulin resistance in Polycystic ovarian syndrome is still controversial. Keeping in view present study was conducted to evaluate the corelation between serum lepin level, body mass index and insulin level in PCOS in North Indian population.

Method: A case control study was conducted in department of biochemistry and department of obstetrics and gynaecology at VMMC & safdarjung hospital, New Delhi. 50 cases diagnosed with PCOS satisfying the Rotterdam criteria were enrolled in the study. 50 Age and sex matched controls were taken excluding patients with any endocrinological disorder or taking hormonal supplementation. Plasma Insulin and Serum Leptin levels were done by commercially available ELISA kit.

Results: The mean leptin level were 27.86 ± 1.33 ng/ml and 12.26± 1.13ng/ml was observed in PCOS patients and controls. Positive correlation was observed in serum leptin level and BMI (r=0.90 p< 0.0001) Mean serum Insulin level was 12.26 mIU/L and 8.26 mIU/L . Obese women with PCOS have significantly higher level of serum Leptin. Correlation between serum leptin level and fasting insulin was insignificant(p>0.05)

Conclusion: Serum fasting Insulin and Serum Leptin levels could serve as an early biomarkers for PCOS complications hence, early intervention could prevent progression of disease to Diabetes and metabolic syndrome.