Symposium 2

Gut, Brain, and Obesity

Chairpersons

Wen-Yuan Lin
China Medical University, Taiwan

Kae Won Cho
Soonchunhyang University, Korea

Speakers

Chih-Yen Chen
National Yang Ming Chiao Tung University, Taiwan

Teppei Fujikawa
UT Southwestern Medical Center, USA

Ki Woo Kim
Yonsei University, Korea

Panel Discussion

Obin Kwon
Seoul National University, Korea

Jaemin Lee
DGIST, Korea

Chih-Yen Chen

National Yang Ming Chiao Tung University, Taiwan

• Education

Period	Affiliation	Position
– **2006**	Institute of Clinical Medicine, National Yang-Ming University School of Medicine, Taipei, Taiwan	Ph.D.
– **1992**	School of Medicine, Taipei Medical University, Taipei, Taiwan	M.D.

• Affiliations / Experience

Period	Affiliation	Position
– **1999-2001**	The Brain-Gut Interaction Laboratory, under the guidance of Professor Yvette Taché, CURE / DDRC & UCLA, Los Angeles, California, USA	Post-Doctoral Fellowship
– **1996-1998**	Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan	Chief Resident
– **1992-1996**	Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan	Rotating Resident

• Committee Memberships

- Chinese Taipei Society for the Study of Obesity (CTSSO)
- Taiwan Association for the Study of Intestinal Diseases (TASID)
- Taiwan Association of Institutional Review Boards (TAIRB)

• Publications

- Guo JY, Chen HH, Lee WJ, Chen SC, Lee SD, Chen CY*. Fibroblast growth factor 19 and fibroblast growth factor 21 regulation in obese diabetics, and non-alcoholic fatty liver disease after gastric bypass. *Nutrients* 14(3): 645
- Wang W, Fann CSJ, Yang SH, Chen HH, Chen CY*. Weight loss and metabolic improvements in obese patients undergoing gastric banding and gastric banded plication: A comparison. *Nutrition* 57: 290-299
- Lee WJ, Chen CY*, Chong K, Lee YC, Chen SC, Lee SD. Changes in postprandial gut hormones after metabolic surgery: a comparison of gastric bypass and sleeve gastrectomy. *Surg Obes Relat Dis* 7(6): 683-690
- Chen CY, Asakawa A, Fujimiya M, Lee SD, Inui A. Ghrelin gene products and the regulation of food intake and gut motility. *Pharmacol Rev* 61(4): 430-481
- Chen CY, Inui A, Asakawa A, Fujino K, Kato I, Chen CC, Ueno N, Fujimiya M. Des-acyl ghrelin acts by CRF type 2 receptors to disrupt fasted stomach motility in conscious rats. *Gastroenterology* 129: 8-25

Symposium 2

Gut Hormone and Brain in Obesity

Chih-Yen Chen (National Yang Ming Chiao Tung University, Taiwan)

Obesity is a major health challenge, and its health risks have been targeted by wide attention. Obesity is primarily a disease of subcortical brain regions which is characterised by the pathognomonic symptoms of excessive hunger and/or reduced satiation after a meal and the pathognomonic sign of increased adiposity. Overcoming obesity is a great task. Benefits are approaching those of gastric bypass, and offer effective prevention of obesity, type 2 diabetes mellitus, and metabolic dysfunction-associated steatotic liver disease (MASLD). Level 1A evidence shows that gastric bypass induces fat loss and improved glucose homeostasis. Obesity is associated with significant disruption in endocrine function, manifesting in changes of gut hormone secretion and insulin secretion, affecting many organ functions in humans. Gut hormones impact food intake, energy balance, and aging process. Plasma levels of gut hormones serve as biomarkers for obesity and related comorbidity in our body.

Gut hormones target brain and adipose tissue. Recent studies imply that hormones, especially gut hormones, may play important roles in improvement of obesity and diabetes remission after bariatric surgery. Four possible mechanisms had been proposed, including the starvation-followed-by-weight loss hypothesis, the ghrelin hypothesis, the lower intestinal (hindgut) hypothesis, and the upper intestinal (foregut) hypothesis. However, no single one of these theories necessarily precludes the others. Ghrelin, obestatin, nesfatin-1, cholecystokinin, gastric inhibitory peptide, glucagon-like peptide-1 (GLP-1), peptide YY, pancreatic polypeptide, and amylin, all have been shown to be involved in the changes of their respective plasma levels and energy balance after bariatric surgery. These gastroenteropancreatic hormones either acts via vagal afferent nerve or blood circulation, or both, on the arcuate nucleus of the hypothalamus (NPY/AgRP and POMC/CART neurons), and the subsequent neuroendocrine changes further regulate food intake, glucose homeostasis, and energy partition and expenditure. In functional magnetic resonance imaging (fMRI) studies, changes in blood oxygen level-dependent (BOLD) signal, enhanced satietygut hormone responses after gastric bypass has been proposed to be a causative mechanism by which anatomical alterations of the gut in obesity surgery modify behavioral and brain reward responses to food cues. Advances in drug development have already lead GLP-1 receptor agonist (Semaglutide) to treat obesity. On the other hand, a longer-acting amylin-analog, cagrilintide, would have even more pronounced weight-loss benefits, and will come to the market. The therapymanipulating gut hormones enables us to bridge the gap between lifestyle therapy and bariatric

Teppei Fujikawa

UT Southwestern Medical Center, USA

• Education

Period	Affiliation	Position
– **2003**	Kyoto University	Ph.D.

• Affiliations / Experience

Period	Affiliation	Position
– **2020-Present**	UT Southwestern Medical Center	Assistant Professor
– **2017-2020**	UT Health San Antonio	Assistant Professor
– **2014-2017**	UT Southwestern Medical Center	Instructor
– **2008-2013**	UT Southwestern Medical Center	Postdoctoral Fellow

• Publications

– Yoshida T, Fujitani M, Farmer S, Harada A, Shi Z, Lee JJ, Tinajero A, Singha AK, Fujikawa T. VMHdm/cSF-1 Neuronal Circuits Regulate Skeletal Muscle PGC1-alpha via the Sympathoadrenal Drive. *Mol Metab*. 101792. Epub 20230824. doi: 10.1016/j.molmet.101792. PMID: 37633515 *Selected as Cover Figure https://www.sciencedirect.com/journal/molecular-metabolism/vol/77

– Fujikawa T. Central regulation of glucose metabolism in an insulin-dependent and -independent manner. *J Neuroendocrinol*. e12941. doi: 10.1111/jne.12941

– Singha, A., Palavicini, JP., Pan, M., Farmer, S., Sandoval, D., Han, X., Fujikawa,T. Leptin Receptors in RIP-Cre25Mgn neurons Mediate Anti-Dyslipidemia Effects of Leptin in Insulin-Deficient Mice. *Frontiers Endocrinology*. 11:588447

– Singha, A.K., Yamaguchi, J., Gonzalez, N.S., Ahmed, N., Toney, G.M., Fujikawa, T. Glucose-Lowering by Leptin in the Absence of Insulin Does Not Fully Rely on the Central Melanocortin System in Male Mice. Endocrinology

– Fujikawa, T., Castorena, C.M., Pearson, M., Kusminski, C.M., Ahmed, N., Battiprolu, P.K., Kim, K.W., Lee, S., Hill, J.A., Scherer, P.E., Holland, L.W., and Elmquist, J.K., SF-1 Expression in the Hypothalamus is Required for Beneficial Metabolic Effects of Exercise. eLife

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Decoding VMH Regulation of Food Intake in Adults

Teppei Fujikawa (UT Southwestern Medical Center, USA)

NR5A1, also known as steroidogenic factor-1 (SF-1), is expressed in the ventromedial hypothalamic nucleus (VMH) within the central nervous system (CNS). Deletion of Nr5a1 in the VMH (VMHNr5a1) in the prenatal or adolescent stage alters energy homeostasis upon high-fat feeding and disrupts metabolic adaptations to exercise, without affecting food intake. There is a conundrum concerning the role of VMH in regulating food intake. The classic studies using VMH-lesion showed that the VMH is key to the regulation of food intake. Intriguingly, a majority of studies investigating effects of deletion of genes in the VMH using Sf-1-BAC-Cre mice suggest that the VMH does not regulate food intake. Recent studies using optogenetics and chemogenetics, however, demonstrate that manipulation of VMH neuronal activities can alter food intake. These "discrepancies" among studies outlined above likely stem from the timing of genetic manipulation, specifically whether it occurs during developmental including adolescent or adult stages. We hypothesize that NR5A1 in the VMH in adults plays a key role in the regulation of food intake. To decipher the role of VMHNr5a1 in the regulation of food intake, we ablated Nr5a1 in the VMH in adults using an adeno-associated virus approach. We found that mice lacking Nr5a1 in the VMH in adults (Adult-VMHΔNr5a1) increase food intake and gain body weight substantially. This is in stark contrast to the prenatal or adolescent manipulation of Nr5a1. Using electrophysiological and RNA omics approaches, we found that deletion of VMH Nr5a1 in adults has profound effects on transcriptional regulation in the hypothalamus, leading to decreases in VMH neuronal activities. These studies highlight the functional differences of NR5A1 in the VMH between adolescents and adults.

Ki Woo Kim

Yonsei University, Korea

• Education

Period	Affiliation	Position
– **2009-2013**	UT-Southwestern Medical Center, Dallas, TX	Postdoctoral Fellow
– **2004-2009**	UT-Southwestern Medical Center, Dallas, TX	Ph.D.

• Affiliations / Experience

Period	Affiliation	Position
– **2023-Present**	Yonsei University College of Dentistry	Professor
– **2018-2022**	Yonsei University College of Dentistry	Associate Professor
– **2013-2018**	Yonsei University Wonju College of Medicine	Assistant, Associate Professor

• Publications

– Astrocytic FoxO1 in the Hypothalamus Regulates Metabolic Homeostasis by Coordinating Neuropeptide Y Neuron Activity. Doan KV, Tran LT, Yang DJ, Ha TTA, Mai TD, Kim SK, DePinho RA, Shin DM, Choi YH, Kim K. W. *Glia*. 71(12): 2735-2752. doi: 10.1002/glia.24448. Epub

– Mitochondria-derived peptide SHLP2 regulates energy homeostasis through the activation of hypothalamic neurons. Kim SK, Tran LT, NamKoong C, Choi HJ, Chun HJ, Lee YH, Cheon M, Chung C, Hwang J, Lim HH, Shin DM, Choi YH, Kim K.W. Nat. *Commun*. 14(1):4321. doi: 10.1038/s41467-023-40082-7

– Primary cilia regulate adaptive responses to fasting. Yang DJ, Tran LT, Yoon SG, Seong JK, Shin DM, Choi YH, and Kim KW. Metab. Clin. *Exp.* 135:155273. doi: 10.1016/j.metabol.2022.155273

– Ventromedial Hypothalamic Primary Cilia Control Energy and Skeletal Homeostasis. Sun JS, Yang DJ, Kinyua AW, Yoon SG, Seong JK, Kim J, Moon SJ, Shin DM, Choi YH, and Kim KW. J. Clin. *Invest*. 131(1):e138107. doi: 10.1172/JCI138107

– FoxO1 regulates leptin-induced mood behavior by targeting tyrosine hydroxylase Metabolism. Son DH, Doan KV, Yang DJ, Sun JS, Kim SK, Kang N, Kang JY, Paik JH, DePinho RA, Choi YH, Shin DM, Kim K.W. Metab. Clin. *Exp*. 91:43-52

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A Microbiota-Derived Short Chain Fatty Acid Targets the Hypothalamus and Regulates Energy Balance

Ki Woo Kim (Yonsei University, Korea)

The microbiota-derived short-chain fatty acid (SCFA) butyrate is known to act beyond the gut to influence host metabolism, including its central nervous system regulation of appetite and energy homeostasis. However, mechanistic insights into central butyrate metabolic actions are undetermined. Here we showed that butyrate directly modulates primary cilia of the agouti-related peptide (AgRP) neurons in the hypothalamic arcuate nuclei to promote its anorexigenic and metabolic effects on glucose homeostasis. Butyrate treatment, either via peripheral or central administration, markedly increased histone acetylation and ciliogenesis in the hypothalamus, suppressing food intake to benefit whole-body metabolism. Disruption of primary cilia in the entire hypothalamus or specifically in the AgRP neurons, but not in the pro-opiomelanocortin (POMC) or ventromedial hypothalamus (VMH) neurons, abolished butyrate metabolic effects. Mechanistically, deletion of primary cilia impaired cellular expression of the butyrate receptor, GPR41/FFAR3, in the AgRP neurons and eradicated its inhibitory action on these neurons.