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Invited Commentary

Comment on Choi *et al.*: High-fat diet decreases energy expenditure and expression of genes controlling lipid metabolism, mitochondrial function and skeletal system development in the adipose tissue, along with increased expression of extracellular matrix remodelling- and inflammation-related genes

In their recent article, Choi *et al.*[1] reported that prolonged ingestion of a high-fat diet (HFD) decreased energy expenditure and expression of genes controlling mitochondrial function as well as skeletal system development in the visceral adipose tissue in mice, and influenced the expression of a series of genes involved in immune and inflammatory responses. Interestingly, they have also demonstrated that HFD down-regulated specific genes involved in lipolysis and fatty acid (FA) metabolism, including those involved in FA activation and oxidation (*Acsm3*, *Acacb*, *Acot4*, *Acadsb*, *Hadh* and *Faah*). Here, we would like to add another layer to the study of Choi *et al.*[1] by focusing on the relationship between HFD and the endocannabinoid system (ECS) *v.* obesity.

Earlier studies have shown that HFD-induced obesity and insulin resistance were associated with an increased activity of the ECS and promotion of the hepatic expression of lipogenic genes, including stearoyl-CoA desaturase-1[2]. Moreover, HFD-induced increase in the hepatic levels of the endocannabinoid anandamide (AEA) has been attributed to the reduced activity of the AEA-degrading enzyme, fatty acid amide hydrolase (FAAH)[2]. Another study has shown that dietary FA composition modulated peripheral endocannabinoid levels in a differential and tissue-specific manner[3]. Consequently, Engeli *et al.*[3] hypothesised that the peripheral ECS remains a promising target for dietary and pharmacological interventions in disease states related to obesity.

HFD-induced changes in the peripheral ECS could have important implications for the pathogenesis of metabolic diseases via 'classical' and 'non-classical' cannabinoid (CB) receptors. The former have already been shown to modulate pancreatic, adipose tissue, skeletal muscle and liver metabolism[4]. For example, in their recent study, Di Marzo *et al.*[5] reported that the ECS undergoes adaptive changes upon feeding HFD, as revealed by altered AEA and CB1 mRNA levels and by different potencies of the FAAH inhibitor AA-5-HT in delaying gastric emptying under this dietary regimen.

Since the pharmacology of 'classical' CB receptors is relatively well studied, it seems interesting to focus on the relationship between HFD and 'non-classical' CB receptors. These 'non-classical' CB receptors, such as GPR30, GPR55, TRPV1 or TRPV4, have been shown to participate in the endocannabinoid and non-CB lipophilic compound-dependent signalling. Now, it may be of interest to the readership to know whether 'non-classical' receptors have also been studied in relation to HFD and obesity.

Aleksandra Sobolewska[1,2]
Marcin Włodarczyk[1,2,3]
Krzysztof Włodarczyk[4]
Maria Wiśniewska-Jarosińska[2]
Jakub Fichna[1]*

[1]*Department of Biochemistry, Medical University of Lodz, Lodz, Poland*

[2]*Department of Gastroenterology, Medical University of Lodz, Lodz, Poland*

[3]*Department of General and Colorectal Surgery, Medical University of Lodz, Lodz, Poland*

[4]*Department of Cardiology, Chair of Cardiology and Cardiac Surgery, Medical University of Lodz, Lodz, Poland*

email jakub.fichna@umed.lodz.pl

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Response to the Commentary by Sobolewska et al. *on Choi* et al.

In our study, *Trpv4* mRNA expression was down-regulated in the adipose tissue of mice fed a high-fat diet compared with those fed a low-fat diet, although there was no significant difference in the mRNA expression of *Gpr30*, *Gpr55* and *Trpv1* in the adipose tissue between the high-fat and low-fat groups (Choi *et al.*[1]). Interestingly, O'Conor *et al.*[2] demonstrated that *Trpv4* deficiency led to obesity and obesity-induced osteoarthritis in high-fat diet-fed mice. Adipocytes of *Trpv4*-deficient mice appeared larger than those of *Trpv4*$^{+/+}$ mice at 10 weeks of age, and adipose-derived stem cells from *Trpv4*-deficient mice had increased adipogenic and osteogenic properties.

However, Ye *et al.*[3] suggested that Trpv4 is a regulator of adipose oxidative metabolism, inflammation and energy homeostasis. *Trpv4*-deficient mice have higher mRNA expression levels of thermogenic and pro-inflammatory genes in the adipose tissue. Therefore, the role of Trpv4 in body fat regulation and obesity is still unclear, and further studies are needed to investigate the relationship between high-fat diet-induced obesity and non-classical receptors, including Trpv4.

Myung-Sook Choi[1,2]
Young-Je Kim[1,2]
Eun-Young Kwon[2]
Jae Young Ryoo[3]
Sang Ryong Kim[3]
Un Ju Jung[1]*

[1]*Department of Food Science and Nutrition, Kyungpook National University, 1370 San-Kyuk Dong Puk-Ku, Daegu 702-701, Republic of Korea*

[2]*Center for Food and Nutritional Genomics Research, Kyungpook National University, 1370 San-Kyuk Dong Puk-Ku, Daegu 702-701, Republic of Korea*

[3]*School of Life Sciences, BK21 Plus KNU Creative BioResearch Group, Kyungpook National University, 1370 San-Kyuk Dong Puk-Ku, Daegu 702-701, Republic of Korea*

email jungunju@naver.com

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