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Regulating Hypothalamus Gene Expression in Food Intake: Dietary Composition or Calorie Density? (*Diabetes Metab J* 2017;41:121-7)

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We appreciate Dr. Koo's interest and comments on our article entitled "Regulating hypothalamus gene expression in food intake: dietary composition or calorie density?" which was published in *Diabetes and Metabolism Journal* [1].

The regulation of appetite and food or energy intake is fundamental to body weight control. The epidemiological evidence that a high intake of dietary fat has long been thought to be implicated in the development of obesity with a positive association with a high-fat (HF), high-energy, dense diet but is not yet definitive [2]. Previously, some studies showed dietary fat has relatively weak effect on satiating effect compared to isoenergetic amounts of carbohydrate (CHO) in most [3], although not all [4]. However, it is not only the macronutrient content of the diet but also the energy content that may be affecting food intake. The energy intake, and hence the satiating effects of fat and CHO, were very similar in HF and high-CHO diets so long as the energy density was the same [5]. These results support our results that calorie density of diet may be more critical factor than fat composition in food intake. However, Dr. Koo's opinions are that polyunsaturated fatty acid (PUFA) increases proopiomelanocortin (POMC) expression [6,7], and saturated fatty acid (SFA) feeding did not alter POMC expression level [8,9]. On the other hand, we reported that purified high SFA or n-3 PUFA significantly increased POMC mRNA expression 2 hours after intragastric administration compared with baseline. The increase in the level of POMC expression was highest in CHO-rich diet group followed by SFA-rich diet group, and the lowest was in n-3 PUFA-rich diet group. The possible reason for the different results might be the different experimental designs and methods between ours and those of other studies [6-9]. We analyzed gene expressions 2 hours after intragastric administration of purified fatty acids dissolved in dimethyl sulfoxide, and after CHO-rich or fat-rich diet feeding *ad libitum* for just 15 hours. On the other hand other studies analyzed gene expressions after long-term diet feeding. While our experiment focused on the acute effects of purified fatty acids and dietary composition on hypothalamic gene expressions, other studies focused on the chronic effects of dietary composition. In a recent report, there was no evidence of differential effects of dietary fat composition on changes in postingestive satiety and energy intake in lean and healthy men [10]. This result is also different from Dr. Koo's opinion.

In addition, Dr. Koo noticed that glucagon-like peptide-1 (GLP-1) reduces food intake [11,12]. GLP-1 response increased with fat-rich meal compared with isocaloric CHO-rich meals in human [13], and dietary fat composition also affected GLP-1 response: unsaturated fatty acids increased GLP-1 more than SFA [14]. Considering that GLP-1 reduces food intake by directly stimulating POMC/cocaine and amphetamine regulated transcript (CART) neurons [11,12], there is a discrepancy with our findings and previous studies [11,12] in that CHO-rich

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meal and SFA increased POMC expression level more than PUFA. We agree with Dr. Koo's opinion that GLP-1 reduces food intake by stimulating POMC/CART neurons. Interestingly, GLP-1 response at early phase (30 minutes) after eating was higher after CHO-rich meal compared with fat-rich meal, and SFA meal caused more GLP-1 response than PUFA meal, but opposite results were observed at late phase (6 hours after eating) (Fig. 2A of [15]). The early phase response of GLP-$1_{AUC(0-2\ hr)}$ was 27% and 23% higher after CHO-rich meal compared with monounsaturated fatty acid (MUFA) and n-6 PUFA meals, respectively (Fig. 2A of [15]). This result suggest that POMC expression by GLP-1 stimulation could be higher in CHO-rich meal group than in fat-rich meal, which is in accordance with our results. There are more evidence that fatty acid composition differentially affected GLP-1 response, but different GLP-1 responses among different diet composition groups was not associated with changes in subjective appetite ratings or changes in energy intake when alterations were made from an acute HF meal to fatty acid composition [16], and GLP-1 response in SFA-rich diet group tended to be somewhat higher than in PUFA-rich diet group at 150 minutes after eating (Fig. 1 of [16]). These results could be in agreement with ours although GLP-1 response was very variable depending on the time period after eating [15,16].

Lastly, Dr. Koo noticed that plasma glucose, free fatty acid, lipid, leptin, and ghrelin levels are very important factors in satiety regulation. The food intake is regulated by physiological signals among the gastrointestinal tract, adipose tissue, and the hypothalamus. It is influenced by behavioral, neuronal, autonomic, nutritional, and endocrine mechanisms [17]. I expect that further study will be required to understand these processes further.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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