

## LETTERS

### The timing of ingestion may influence the effect of nonnutritive sweeteners on cardiometabolic health: a potentially overlooked factor

We appreciate the recent review for non-nutritive sweeteners by Azad and colleagues.<sup>1</sup> We agree with the important updated comments by Sievenpiper and colleagues,<sup>2</sup> who pointed out the issue of comparators in randomized controlled trials, and the high risk of potential bias and reverse causality in prospective cohort studies. However, other overlooked factors may also influence the effect of nonnutritive sweetener on cardiometabolic risks.

When nonnutritive sweetener is consumed in the fasting state, but not in the postprandial state, nonnutritive sweetener more likely affects the gut membrane and receptors in the gut. Nonnutritive sweetener may stimulate secretion of incretins,<sup>3,4</sup> which can prevent overeating and occasionally lead to anorexia. Furthermore, dissociation between sweet taste and energy or plasma glucose may occur.<sup>5,6</sup> Hypoglycemia could occur in the condition of long-term fasting, possibly with the concomitant effect of incretins. We consider that the mechanisms of hypoglycemia, increased consumption of food and obesity may contribute, at least in part, to the conflicting and unexpected results of many clinical studies.

In the postprandial state, possible interference of nonnutritive sweetener with extraoral receptors and potential consequent adverse effects, including hypoglycemia, could be attenuated. This is because extraoral receptors are more likely to be occupied with substances in foods and a large amount of food may simultaneously keep nonnutritive sweetener from contacting the mucous membrane of the gut. Moreover, because levels of plasma glucose increase after regular meals, the dissociation mentioned above is unlikely to occur. Further

clinical studies evaluating these issues are required to investigate the potential benefits or adverse effects of consumption of nonnutritive sweetener.

#### Kei Nakajima MD PhD

Professor, School of Nutrition and Dietetics, Faculty of Health and Social Services, Kanagawa University of Human Services, Yokosuka, Kanagawa, Japan; Visiting Professor, Department of Endocrinology and Diabetes, Saitama Medical Center, Saitama Medical University, Kawagoe, Saitama Japan

#### Taizo Iwane RD PhD

Researcher, School of Nutrition and Dietetics, Faculty of Health and Social Services, Kanagawa University of Human Services, Yokosuka, Kanagawa, Japan

#### Ryoko Higuchi RD

Assistant Professor, School of Nutrition and Dietetics, Faculty of Health and Social Services, Kanagawa University of Human Services, Yokosuka, Kanagawa, Japan

■ Cite as: *CMAJ* 2017 November 20;189:E1427. doi: 10.1503/cmaj.733416

#### References

1. Azad MB, Abou-Setta AM, Chauhan BF, et al. Non-nutritive sweeteners and cardiometabolic health: a systematic review and meta-analysis of randomized controlled trials and prospective cohort studies. *CMAJ* 2017;189:E929-39.
2. Sievenpiper JL, Khan TA, Ha V, et al. The importance of study design in the assessment of non-nutritive sweeteners and cardiometabolic health [letter]. *CMAJ* 2017;189:E1424-5.
3. Brown RJ, Rother KI. Non-nutritive sweeteners and their role in the gastrointestinal tract. *J Clin Endocrinol Metab* 2012;97:2597-605.
4. Chan CB, Hashemi Z, Subhan FB. The impact of low and no-caloric sweeteners on glucose absorption, incretin secretion, and glucose tolerance. *Appl Physiol Nutr Metab* 2017;42:793-801.
5. Pepino MY, Bourne C. Non-nutritive sweeteners, energy balance, and glucose homeostasis. *Curr Opin Clin Nutr Metab Care* 2011;14:391-5.
6. Romo-Romo A, Aguilar-Salinas CA, Gómez-Díaz RA, et al. Non-nutritive sweeteners: evidence on their association with metabolic diseases and potential effects on glucose metabolism and appetite. *Rev Invest Clin* 2017;69:129-38.

**Competing interests:** None declared.