Response to Comment on: Teeuwisse et al. Short-Term Caloric Restriction Normalizes Hypothalamic Neuronal Responsiveness to Glucose Ingestion in Patients With Type 2 Diabetes. Diabetes 2012;61:3255–3259

Ralph L. Widya,[1] Hanno Pijl,[2] and Jeroen van der Grond[1]

We wish to thank Drs. Heni, Kullmann, and Fritsche (1) for their interesting comments on our article (2). Their findings that plasma glucose and insulin are associated with hypothalamic activity (3,4) are of importance for the clarification of the complex relationship between the brain and feeding. We agree that glucose and insulin levels are potential triggers for the hypothalamic response to glucose ingestion. This response can be accurately assessed using functional magnetic resonance imaging.

However, the importance of plasma glucose in the context of hypothalamic activity after glucose ingestion is disputable. Although the exact onset of the hypothalamic signal decrease cannot be determined accurately due to image artifacts associated with drinking, it starts before the completion of glucose ingestion. This is well before most of the glucose has entered the bloodstream. Moreover, an oral glucose challenge resulted in a more profound hypothalamic signal decrease compared with an intravenous glucose challenge, despite lower plasma glucose levels. We therefore believe that plasma glucose levels do not play an important role in the response of the hypothalamus to glucose ingestion.

More important is the role of insulin. Insulin receptors are expressed by many key neurons located in the hypothalamus, which are implicated in the control of food intake and behavior. Nasal administration of insulin, as performed by Kullmann et al. (4), is an elegant method to investigate selective insulin actions on the human brain. Kullmann et al. demonstrated an intranasal insulin effect on hypothalamic activity (4). In addition, insulin may be implicated in modifying the reward and prefrontal circuitry of the human brain, thereby possibly blunting the rewarding properties of food (4). These findings suggest an important role of insulin action in the immediate hypothalamic response observed after glucose ingestion. However, a decisive contribution of insulin could not be demonstrated earlier. Smeets et al. (5) showed that despite the fact that insulin concentrations rise in response to glucose as well as to maltodextrin (nonsweet carbohydrate) ingestion, the hypothalamic functional magnetic resonance imaging signal decreases only after glucose ingestion.

Glucose ingestion triggers intestinal cells to release several hormones. These gut peptides signal food intake to the appetite-regulating circuits of the brain and act in the hypothalamus to induce satiety. It is conceivable that an integrated set of various metabolic and endocrine cues, including glucose, insulin, and gut peptides, is critical for the hypothalamic response to nutrient ingestion. Moreover, the role of other yet unknown factors cannot be excluded.

ACKNOWLEDGMENTS

No potential conflicts of interest relevant to this article were reported.

REFERENCES

1. Heni M, Kullmann S, Fritsche A. Comment on: Teeuwisse et al. Short-term caloric restriction normalizes hypothalamic neuronal responsiveness to glucose ingestion in patients with type 2 diabetes. Diabetes 2012;61:3255–3259 (Letter). Diabetes 2013;62:e5. DOI: 10.2337/db13-0054
2. Teeuwisse WM, Widya RL, Paulides M, et al. Short-term caloric restriction normalizes hypothalamic neuronal responsiveness to glucose ingestion in patients with type 2 diabetes. Diabetes 2012;61:3255–3259
3. Heni M, Kullmann S, Ketterer C, et al. Differential effect of glucose ingestion on the neural processing of food stimuli in lean and overweight adults. Hum Brain Mapp. 10 January 2013 [Epub ahead of print]
4. Kullmann S, Frank S, Heni M, et al. Intranasal insulin modulates intrinsic reward and prefrontal circuitry of the human brain in lean women. Neuroendocrinology 2013;97:176–182
5. Smeets PA, de Graaf C, Stafleu A, van Osch MJ, van der Grond J. Functional magnetic resonance imaging of human hypothalamic responses to sweet taste and calories. Am J Clin Nutr 2005;82:1011–1016

From the [1]Department of Radiology, Leiden University Medical Center, Leiden, the Netherlands; and the [2]Department of Endocrinology and Metabolism, Leiden University Medical Center, Leiden, the Netherlands.
Corresponding author: Jeroen van der Grond, j.van_der_grond@lumc.nl.
DOI: 10.2337/db13-0296