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

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The functional magnetic resonance imaging study by Teeuwisse et al. (1) investigated the effect of caloric restriction on glucose responsiveness of the hypothalamus in patients with type 2 diabetes. In these patients, an oral glucose test does not decrease hypothalamic activity (2), a reaction observed in healthy persons (3). The authors showed that a 4-day very-low-calorie diet (450 kcal/day) was sufficient to normalize the physiological hypothalamic response.

On the basis of animal and human findings, Teeuwisse et al. discussed very comprehensively the possible underlying mechanisms of the hypothalamic response to glucose ingestion, such as glucose sensing in the hypothalamus. Although increasing plasma glucose did not significantly correlate with the hypothalamic activity in their study, we identified such a correlation in a recent study 30 min after comparable glucose ingestion in healthy humans (4), presumably because we studied more than twice the number of participants. We therefore propose that glucose could be one factor to modulate hypothalamic activity in humans.

Another possible factor discussed by Teeuwisse et al. is the influence of the hormone insulin. Neither in the study by Teeuwisse et al. nor in our recent study did increasing insulin concentration during an oral glucose tolerance test significantly correlate with hypothalamic activity. However, in a separate study with intranasal insulin delivery possibly resulting in higher cerebral insulin concentrations, we showed insulin to reduce hypothalamic activity in humans (5,6). Of interest, this insulin response in the hypothalamus could be important for the entire body since it was tightly correlated to changes in whole-body insulin sensitivity (6). Detailed studies in animals found distinct distribution of insulin- and glucose-responsive neurons in hypothalamic nuclei (1,7,8). Hence, there are possible effects on insulin-responsive hypothalamic neurons during an oral glucose tolerance test, but the strong reaction of glucose-sensing neurons might mask insulin effects and hinder their detection using the currently applied functional magnetic resonance imaging techniques.

We would like to emphasize the importance of the finding that hypothalamic glucose response can be improved in patients with type 2 diabetes. Given the regulatory effects of the brain on peripheral metabolism (6,8) and the further development of body weight (9), this mechanism could have important impacts on the entire body. We strongly support the claim of Teeuwisse et al. that further research in the area of neurometabolism is urgently needed to better understand the basic underlying mechanisms and to develop tools to favorably influence them.

ACKNOWLEDGMENTS

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

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DOI: 10.2337/db13-0054