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RESPONSE TO COMMENT ON HENI ET AL.

Central Insulin Administration Improves Whole-Body Insulin Sensitivity via Hypothalamus and Parasympathetic Outputs in Men. Diabetes 2014;63:4083–4088

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We wish to thank Dhindsa et al. (1) for their thoughtful comments on our article published in *Diabetes* (2). In our study, intranasal application of insulin to the human brain improved peripheral insulin sensitivity in lean but not obese men (assessed as glucose infusion rate during hyperinsulinemic-euglycemic clamp). This improvement was significantly correlated to hypothalamic insulin responsiveness as well as to parasympathetic outflows.

Dhindsa et al. (1) provide the interesting hypothesis that obese humans could be resistant to "brain outputs" that regulate peripheral insulin sensitivity. Indeed, such a mechanism might contribute to the resistance of our obese participants to the insulin-sensitizing effect of intranasal insulin. We agree that resistance of peripheral tissues to brain outputs, such as the autonomic nervous system, is well conceivable. In line with this hypothesis, altered activity of mainly the parasympathetic nervous system is well known in obesity (see ref. 3). However, we are not aware of studies on the transmission of autonomic nerves on target organs such as the liver in the context of obesity.

On the other hand, data from our group and others show that brain insulin resistance is present in obesity (reviewed in refs. 4 and 5). We therefore believe that altered brain responsiveness to nasal insulin has a major contribution to our current findings in obese participants.

Of note, Figs. 3 and 4 in our article (2) are both adjusted for BMI. This allowed the inclusion of obese subjects into the models to enhance statistical power. Hence, these figures do not indicate that lean and obese participants reacted equally to nasal insulin in terms of hypothalamic activity and high-frequency band activity. Unfortunately, our subgroups were too small to statistically address differences between the two weight groups for those measurements.

We would like to thank Dhindsa et al. (1) for emphasizing that nasal insulin was shown to affect free fatty acid (FFA) levels (6), a mechanism that could indeed contribute to the regulation of peripheral insulin sensitivity. To address this issue, we analyzed FFA concentrations during our study. Initiation of the hyperinsulinemic clamp rapidly caused a dramatic decline in plasma FFAs from a baseline level of 421 $\pm$ 31 μmol/L to 96 $\pm$ 12 μmol/L before spray application. Intranasal insulin did not further reduce FFA concentrations; there were no significant differences between intranasal insulin and placebo administration (MANOVA, $P = 0.7$ for lean and $P = 0.9$ for obese participants). These results indicate a marked suppression of lipolysis by the intravenous insulin infusion during the clamp that cannot be further influenced by intranasal insulin. Thus, brain insulin action regulates lipolysis under fasting conditions (6), a mechanism that is diminished or even absent in the presence of systemic hyperinsulinemia. Hence, altered FFA concentrations cannot explain the regulation of peripheral insulin sensitivity in our study (2).

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Just as Dhindsa et al., we are looking forward to forthcoming clinical studies on the exciting topic of how the brain regulates whole-body metabolism.

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

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