

Results demonstrated that the intervention that focused on illness perception issues had significant positive effects on exercise and dietary behaviors as compared with the control group, when measured directly after the intervention. The intervention had similar positive short-term effects on increasing perceptions of T2DM as a serious condition and in activating partners' levels of support. While none of these effects were observed as significant in the 6-month follow-up, significant increases in feelings of empowerment regarding T2DM management as compared with the control group were sustained for 6 months following the intervention sessions.

## Exenatide Increases Glucose Uptake in Brain Areas Involved in Glucose Homeostasis and Food Intake

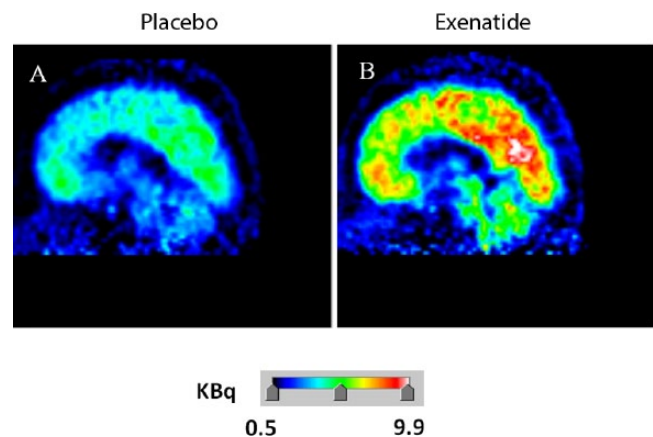
Written by Dennis Bittner

Amalia Gastaldelli, PhD, Research Director of the Cardiometabolic Risk Unit at the Institute of Clinical Physiology, CNR, Pisa, Italy, and Adjunct Associate Professor at the University of Texas Health Science Center, San Antonio, Texas, USA, presented results from the Effect of Exenatide on Brain, Adipose Tissue, Pancreas, and Liver Function study [NCT01588418], of which she was the principal investigator. This is a phase 4 clinical trial that aimed to evaluate the effect of a single injection of exenatide (a glucagon-like peptide-1 [GLP-1] agonist) on cerebral glucose metabolism during an oral glucose tolerance test (OGTT).

GLP-1 is secreted in response to food ingestion. The molecule stimulates insulin secretion, suppresses glucagon secretion, and delays gastric emptying [Campbell JE, Drucker DJ. *Cell Metab* 2013; Nauck et al. *Diabetologia* 2011; Holst JJ. *Curr Opin Pharmacol* 2013]. GLP-1 also has effects outside the pancreas, including suppression of appetite [Gejl et al. *Basic Clin Pharmacol Toxicol* 2014]. The action of GLP-1 on brain glucose metabolism has been hypothesized but has not yet been established [Alvarez et al. *J Neurochem* 2005]. A few studies have looked for effects of GLP-1 on human brain metabolism [Pannaciulli et al. *Neuroimage* 2007; Lerche et al. *Diabetes* 2008; Gejl et al. *J Cereb Blood Flow Metab* 2012], but none of these examined response to a glucose load.

In this phase 4 clinical trial, a total of 15 men, either without diabetes and with impaired glucose tolerance or with newly diagnosed type 2 diabetes mellitus (T2DM) at screening, each underwent 2 double-blind studies in randomized order consisting of subcutaneous injection of

Figure 1. Effect of Exenatide on Glucose Levels in the Brain



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exenatide 5  $\mu$ g or placebo 30 minutes before OGTT. Brain imaging was performed by positron emission tomography beginning 60 minutes after intravenous administration of the radioactive glucose analog  $^{18}$ F-FDG simultaneous with oral glucose 75 g and [U- $^{13}$ C] glucose 1.5 g.

Patients who received exenatide displayed about 40% more glucose uptake in the brain overall, as well as in the frontal, temporal, parietal, and occipital lobes. On average, glucose was markedly higher in areas of the brain known to be involved in glucose homeostasis, such as the limbic system, insula, and putamen. A similar trend was seen for areas associated with the food-intake reward system, with higher uptake in the orbitofrontal cortex, the thalamus, the anterior and posterior cingulate, and, again, the putamen and limbic system (Figure 1;  $P < .05$ ). Dr Gastaldelli noted that uptake in the hypothalamus, on the contrary, was distinctly lower.

Dr Gastaldelli said that the question of whether endogenous glucose production (EGP) is controlled by the brain is still a matter of debate and that the researchers had also looked for clues on the topic of EGP regulation by the brain in the study data. Although a correlation between oral glucose rate of appearance and glucose uptake in areas implicated in glucose homeostasis with exenatide treatment was noted ( $R^2 = 0.642$ ;  $P < .009$ ), no correlation between suppression of EGP and cerebral glucose uptake in the areas implicated in glucose homeostasis was observed.

In conclusion, Dr Gastaldelli stated that, overall, the results of the trial demonstrate the profound effect that exenatide exerts on cerebral glucose metabolism following ingestion of an oral glucose load.