TRANSLATIONAL ANALYSES OF INGESTIVE BEHAVIOR AFTER GASTRIC BYPASS

After Roux-en-Y gastric bypass (RYGB), patients decrease: appetite, caloric intake, body weight, and glycemia, all of which are maintained long-term. This is a large reason why it has become a popular treatment for morbid obesity and Type 2 diabetes mellitus (T2DM). However, a major unresolved issue is whether, after RYGB, patients choose to eat less foods that are high in fat and sugar in favor of lower energy dense alternatives such as vegetables. If true, this could conceivably contribute to improved body weight and glycemia. Disparities among studies on food selection and intake are likely due to the almost complete reliance on self- reported food intake which is vulnerable to inaccuracy. This controversy can best be resolved by complementing existing findings with direct measures of target behaviors in humans that can also be applied to animal models and vice-versa. The proposed experiments will extend the published and preliminary findings suggesting that RYGB alters food preferences without ostensibly changing food palatability. Such changes in food selection alone have been postulated to benefit patients with obesity and/or T2DM and this may be an under-investigated means by which RYGB improves maintenance of body weight and glycemic control. Direct measures in both rats and humans after RYGB will be used to test the hypothesis that the selection and intake of foods varying in fat content and glycemic index, as well as the pattern of ingestion within and across meals, changes in a manner that leads to beneficial outcomes on body weight. While the apparent progressive changes in food preference after RYGB in the rat model strongly suggest learning, such experience-based changes could be driven by either food aversion (changed palatability) or food avoidance (unchanged palatability). Evidence disambiguating these learning processes is lacking, and the proposed experiments are designed to explicitly distinguish between these important and conceptually distinct behavioral mechanisms. The exaggerated pleiotropic gut hormone response to RYGB has been the most promising lead to a physiologic mechanism underlying the changes in feeding, weight loss, and glycemic control. One gut hormone in particular, glucagon like peptide-1 (GLP-1) has been a target in pharmacological interventions in the management of T2DM and is implicated in feeding satiation. Accordingly, the somatostatin analogue Octreotide will be used to block the pleiotropic gut hormone response to RYGB in translational experiments to interrogate the role of these endocrine processes in the progressive changes in ingestive behavior observed. In other experiments, the GLP-1 receptor will be selectively targeted by the antagonist Exendin-9. This scientific alliance is made possible through the US-Ireland R&D Partnership Program which is allowing this established international research team to continue to apply their complementary expertise in the service of addressing fundamental questions that can help guide future research in the treatment and management of obesity and T2DM.

In addition to its effects on body weight, Roux-en-Y gastric bypass (RYGB) reduces cancer and cardiovascular mortality and has beneficial effects on Type 2 diabetes mellitus (T2DM) and it has been postulated that the long-term weight loss and glycemic control after RYGB can be partly explained by the shift in consumption from high fat and sugary foods to low fat and low glycemic alternatives. The interaction of RYGB and food selection, however, remains to be tested with the direct measures proposed here. This research will explore the behavioral and physiological mechanisms underlying RYGB-induced alterations in patterns of food selection to contribute to the effort to develop less invasive interventions to achieve similar clinical benefits.