CNS Integration of Systems Metabolism: Target Opportunities for Diabetes Prevention and Therapy

Matthias H. Tschöp* & Richard DiMarchi#

*Arthur Russell Morgan Chair of Medicine, Metabolic Disease Institute & Diabetes and Obesity Centre, University of Cincinnati, OH, USA
#Gill Professor of Biochemistry, Indiana University, IN, USA

Numerous gut hormones have been reported to affect food intake, metabolism and body weight, mostly via modulation of specific target circuitry in the CNS. Bariatric surgery interventions represent still the only curative approach for morbid obesity and show promise for the treatment of diabetes. Efficient types of bariatric surgeries cause considerable changes in gut hormone patterns, which are thought to be at least in part of mechanistic relevance for metabolic benefits. We are working toward utilization of several afferent gut hormones as an indirect way of modulating CNS control centers of metabolism and ultimately design new combination therapy approaches. Recently we described a series of potent single molecule glucagon-GLP1 co-agonists with a molecular weight and structure similar to glucagon. These drug candidates were sufficiently potent to eliminate obesity and insulin resistance in diet-induced rodent models of obesity. In separate studies, we developed a similar sized single molecule co-agonist with full potency at the GLP1 and the GIP receptor. As expected, this molecule impressively increased insulin sensitivity in DIO rodent models. Unexpectedly, GLP1-GIP single molecule co-agonists also cured obesity using this pre-clinical model, in spite of earlier reports that GIP-R agonism may have anti-lipolytic effects. In parallel we tested new activation blockers of the adipogenic stomach hormone ghrelin, novel combinations of adipokines with liver factors or gut hormones as well as previously unexplored combinations of cannabinoid and opioid system components with promising results. In summary, our results provide encouraging support for the notion that indirect targeting of key CNS control centers via afferent hormone signals may offer a superior, safe and effective way to prevent and treat the metabolic syndrome.