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Extrapancreatic Effects of GLP-1 and Other Incretins

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The discovery of Glucagon-like peptide 1 (GLP-1) has prompted an important series of advances in our understanding of how the gut and the pancreas interact to regulate the physiology of food ingestion. GLP-1 partially accounts for the incretin effect, whereby orally ingested carbohydrates produce an augmented pancreatic islet hormone response compared to the same amount of carbohydrate delivered intravenously; more generally, GLP-1 and related gut peptides are now understood to integrate food absorption and pancreatic islet function. These discoveries have led to important advances in the clinical care of diabetes, with 2 classes of drugs (and an expanding set of choices within each class) that work through the GLP-1 system now available for the treatment of diabetes.

GLP-1 is an evolutionarily ancient hormone, with analogs or paralogs present in vertebrate species and fish. However, the functions of GLP-1 appear to differ among species, and even in higher vertebrates there appear to be a variety of physiologic functions for GLP-1. The existence of the classical GLP-1 receptor in tissues outside the entero-endocrine axis has been recognized, including the heart, the kidney and the brain. The physiologic roles of GLP-1 in these and other locations have been the subject of an expanding interest in the various extrapancreatic functions of GLP-1.

The current issue of Reviews in Endocrine and Metabolic Disorders includes state-of-the-art reviews of the major recognized extrapancreatic functions of GLP-1. These include manuscripts exploring the contributions of GLP-1 to the regulation of appetite and weight, and an exploration of the role that GLP-1 may play in producing or maintaining the weight loss associated with weight loss surgery. These phenomena are not just of academic interest regarding the physiology of energy balance, but rather provide us with opportunities to better understand the systems at work and highlight the potential to use GLP-1 based therapies to modify weight and energy balance. Interestingly, GLP-1 may be one of many host axes that are affected by, and in turn affect, the gut microbiota and the increasingly recognized symbiotic phenomena that contribute to human gut physiology and pathophysiology. Papers reviewing the effects of GLP-1 in the kidney and the heart demonstrate that GLP-1 is an important contributor to the regulation of whole-body sodium balance, and contributes of GLP-1 to the regulation of hemodynamics. Perhaps the most exciting therapeutic advances may come from the application of GLP-1 based treatments for the treatment of myocardial or cerebral ischemia, and we present papers explaining the genesis of this idea and reviewing the current evidence.

Safe and effective GLP-1 based treatments have been developed and are approved for the treatment of human diabetes (and likely also for weight management in the near future). These agents are primed for deployment in other realms of disease, although the effective dosing and achievable treatment benefits remain to be established. In the near term these agents may come to be used for stroke and myocardial infarction, but possible uses in other conditions abound and the barriers to testing are comparatively low. Therefore it is possible that in the future GLP-1 based treatments may be as widely used for extrapancreatic benefits as for treatment of diabetes. Welcome to the future!