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Modulation of receptor signaling by metabolic environment

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Obesity is a global health epidemic and is associated with comorbidities such as type 2 diabetes and cardiovascular disease. Given the high cost and various health risks associated with the surgical treatment of obesity, additional pharmacologic therapeutic options with improved long-term efficacy and reduced adverse side effects are needed. In the gastrointestinal tract, peptide hormones are released in response to digestion and absorption and serve as regulatory factors of energy homeostasis. Cholecystokinin (CCK) is a gastrointestinal polypeptide hormone released from enteroendocrine I cells located primarily in the proximal small intestine. Released to a larger degree in response to digestive products of dietary protein and fat, and to lesser extent in response to carbohydrates, CCK binds to its receptors located in the periphery, as well as the brain (1). Although there are 2 types of G protein–coupled (GPCR) CCK receptors (CCKRs), they are distributed in a region-specific manner with CCK type 1 receptors (CCK1Rs) located on vagal afferent fibers as well as other peripheral sites, whereas CCK type 2 receptors (CCK2Rs) are localized in the brain and in the stomach where they function as gastrin receptors (2, 3). Although these 2 receptors share ~50% homology, binding to CCK1Rs requires a unique sulfated tyrosine, which allows for high-affinity binding and biological activity. Binding of CCK agonists to CCK1Rs on vagal afferent fibers that innervate the stomach and small intestine promotes satiety by reducing meal size and duration (4). Furthermore, CCK1R antagonists increase meal size; and the absence of CCK1Rs, as is the case with CCK1R knockout mice or the Otsuka Long Evans Tokushima Fatty rat, which lack CCK1Rs due to a spontaneously occurring gene deletion, results in alterations in food intake with chronic increases in meal size (5, 6).

Previously, it was shown in a hamster-derived ovarian cell line that variations in membrane cholesterol content resulted in conformational changes to the CCK1R, thereby altering CCK responsivity (7). Therefore, cellular environment may be a determining factor of receptor function and subsequent efficacy of a peptide (8, 9). In this issue of the Journal, Desai et al. (10) postulated that the CCK1R microenvironment, as may be altered in metabolic syndrome or obesity, may correlate with CCK responsiveness. The authors developed a novel experimental strategy whereby they inserted wild-type human CCK1Rs into an adenoviral plasmid vector for subsequent transduction in subject-derived leukocytes. This allowed for the study of CCK1R efficacy in subject-derived cellular microenvironments and the correlation with metabolic biomarkers. The subject population was recruited from the Sangre Por Salud Biobank and consisted of a predominantly Hispanic population of 112 subjects. Men and women varying in age from 18 to 85 y were recruited for the study. Additional data on subject cardiometabolic health and lipid profiles were collected to allow for the classification of metabolic health after the determination of CCK sensitivity. To determine CCK stimulus-activity coupling, subject-derived leukocytes that express functional wild-type CCK1Rs were exposed to varying CCK1R-agonist (CCK-8) concentrations, and intracellular calcium release was measured. These EC_{50} values, which denote the half-maximal effective concentration of CCK agonist, were used to generate a sigmoidal dose-response curve, and CCK response was then correlated with metabolic phenotyping variables of the subject population. Based on the data, the authors developed a predictive model of CCK efficacy on the basis of the correlation of lipid profiles with EC_{50} values. Interestingly, differing lipid profiles as found in normal-weight compared with obese subjects correlated with CCK efficacy, such that hypertriglyceridemia served as a predictor of reduced response to CCK in normal-weight subjects, whereas high concentrations of cellular cholesterol correlated with reduced CCK efficacy in obese subjects. In diabetic subjects, elevated glycated hemoglobin concentrations, which signal elevated blood glucose concentrations and are used as a measure of diabetes management, correlated with reduced CCK sensitivity. Given the wide range of contributing factors, the authors conclude that multiple biomarkers are necessary to predict CCK therapeutic efficacy and response may vary with the clinical characterization of the patient. In conclusion, this study suggests that differences in membrane cholesterol composition are variable and have profound implications for subsequent pharmacologic intervention. Therefore, additional studies that focus on patient biomarkers may serve as valuable considerations for clinicians when determining the therapeutic efficacy of pharmacologic treatment in individualized patient care.

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Currently, there are no CCK1R agonists that are approved for the treatment of obesity. Side effects such as nausea, cramping, and diarrhea are important factors for consideration in the use of current CCK1R-agonist drug candidates because improvements in weight management have been minimal. Thus, the findings presented by Desai et al. raise several important research questions and considerations. Because elevated cellular cholesterol can influence CCK efficacy through the possible modification of the CCK1R structure, promoting endogenous CCK1R function through changes in the receptor environment or receptor itself may prove fruitful in obesity drug development. First, although the authors showed that serum cholesterol concentrations do not correlate with cellular cholesterol concentrations, additional biochemical lipid markers, such as serum triglycerides, HDL cholesterol, and LDL cholesterol, do correlate in the case of normal-weight and obese patients. Therefore, if drug efficacy in the case of CCK and other peptide receptor agonists depends on cellular membrane environment, as the authors suggest in their conclusions, thorough metabolic profiling of patients may serve as a reliable toolkit for clinicians in determining effective treatment plans for their patients. Next, a potential avenue for drug development may be in the individual improvement in CCK1R function and signaling through the discovery and screening of CCK1R modulators (9). As the authors suggest, the identification of positive allosteric modulators, which can bind to the receptor to improve function without possessing inherent agonist activity, may thereby improve endogenous CCK and CCK1R activity or perhaps decrease the effective dose of other CCK1R agonist drug compounds. Despite these complications, the fact that CCK administered on its own or in combination with other gastrointestinal and adiposity-derived peptides (11) has profound effects on satiety through the modulation of meal size and duration signals the importance of developing a reliable CCK1R agonist with minimal side effects in the treatment of obesity.

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