Chapter 14

CIRCULATING GHRELIN LEVELS IN PATHOPHYSIOLOGICAL CONDITIONS

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Abstract: Circulating levels of ghrelin, are regulated by short-term factors pertaining to food ingestion and longer-term factors pertaining to body weight. The short-term, or prandial, regulation is manifest as marked increases in ghrelin levels before each meal and decreases after food is consumed. This temporal pattern implicates ghrelin as a contributor to pre-meal hunger and the initiation of individual meals. Long-term, body weight-related regulation of ghrelin results in a negative relationship between ghrelin levels and numerous measures of body size. This association and several other findings suggest that ghrelin may participate not only in the short-term control of meal patterns but also in overall body-weight regulation. Ghrelin fulfills all of the established criteria to be an “adiposity signal” that senses the status of body-fat stores and communicates this information to the brain, which activates compensatory changes in appetite and energy expenditure designed to maintain homeostasis. Ghrelin levels vary in response to alterations in energy balance, increasing with weight loss and thus potentially contributing to the compensatory hyperphagia triggered by negative energy balance. The opposite is true for weight gain. Most of the alterations of circulating ghrelin levels in pathophysiological conditions can be viewed as adaptive responses to the body-weight perturbations in these disorders. The only known exception is Prader-Willi syndrome, a condition in which hyperghrelinemia may play a primary, causal role driving hyperphagia and obesity. These patients represent logical subjects in whom first to test the efficacy of ghrelin-blocking agents to treat obesity. Low fat diets promote modest weight loss without triggering the normal compensatory increase in ghrelin levels, and gastric bypass surgery can suppress (or at least constrain) ghrelin levels in most cases. The impact of these interventions on circulating ghrelin may contribute to their weight-reducing effects.

Key words: obesity, body-weight regulation, Prader-Willi syndrome, gastric bypass, anorexia
1. INTRODUCTION

Circulating levels of the orexigenic hormone, ghrelin, are regulated by short-term factors pertaining to food ingestion and longer term factors pertaining to body weight. The short-term, or prandial, regulation is manifest as marked increases in ghrelin levels before each meal and decreases after food is consumed (1-4). This temporal pattern, together with several other observations (reviewed in Ref. 5), implicates ghrelin as a possible contributor to pre-meal hunger and the initiation of individual meals. Long-term, body weight-related regulation of ghrelin results in a negative relationship between ghrelin levels and numerous measures of body size (6-12). This association and several other findings suggest that ghrelin may participate not only in the short-term control of meal patterns but also in overall body weight regulation (5). Ghrelin fulfills all of the established criteria to be an “adiposity signal” that senses the status of body fat stores and communicates this information to the brain, which responds to alterations in energy stores with compensatory changes in appetite and energy expenditure designed to resist such changes (13). As predicted for an adiposity signal, ghrelin levels vary in response to alterations in energy balance, increasing with weight loss and thus potentially contributing to the compensatory hyperphagia triggered by negative energy balance (5). The opposite is true for weight gain (14).

Most of the alterations of circulating ghrelin levels that accompany pathophysiological conditions are consistent with ghrelin’s proposed role as an adiposity signal, and can be viewed as adaptive responses to the body weight perturbations that are caused by these disorders. The only known exception is Prader-Willi syndrome (PWS), a condition in which hyperghrelinemia may play a primary, causal role driving hyperphagia and obesity. People with this disorder represent logical subjects in whom first to test the efficacy of ghrelin-blocking agents to treat obesity. Low fat diets promote modest weight loss without triggering the normal compensatory increase in ghrelin levels, and gastric bypass surgery can suppress (or at least constrain) ghrelin levels in most cases. The impact of these interventions on circulating ghrelin may contribute to their weight reducing effects.

2. PRANDIAL GHRELIN REGULATION AND POSSIBLE ROLES FOR GHRELIN IN MEAL INITIATION

Meal time hunger is a common, daily experience, yet the molecular determinants of this sensation remain enigmatic despite decades of research