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A short-term dynamical model for ghrelin

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Abstract:
Ghrelin, a peptide hormone, occupies a crucial role in food intake control. Differently from other hormones contributing to energy homeostasis, usually exerting their regulating action by signaling satiety (e.g. leptin), ghrelin is known to stimulate appetite and, in general, to upsurge the propensity of animals to seek out food and start eating. Medical and experimental literature has shown that approximately 70-80% of ghrelin production occurs in the stomach, whilst the great part of ghrelin control, leading to ghrelin suppression soon after a meal administration, is exerted by signals originated in the small intestine. This note proposes a mathematical model for ghrelin dynamics, focusing the attention on its short-term 24 hours dynamics. The proposed model conforms to the established physiology by introducing a minimal multi-compartmental structure of the gastrointestinal tract. Model parameters are set in order to fit plasma ghrelin concentration data taken from the literature, related to an experiment in humans: simulation-based ghrelin predictions provide promising results if compared to real data. Besides to offer a proper description of the short-term ghrelin dynamics, the model can be thought of as a module of a bigger multi-compartmental structure, aiming to account for the "web of hormones" (including, e.g., leptin and insulin) related to food intake and energy homeostasis.

Keywords: Mathematical Physiology; Ghrelin; Energy Homeostasis

1. INTRODUCTION

Body weight control occurs according to physiological mechanisms properly balancing energy expenditure with food intake. Prolonged energy imbalance in favor of adipose tissue accumulation usually favors obesity, a body weight dysregulation precursor of many chronic diseases (e.g. diabetes), Flier (2004); Kahn et al. (2006). Relevant literature has highlighted the role of numerous endocrine food intake regulators, such as cholecystokinin, peptide YY, glucagon-like peptide-1 (GLP-1), leptin, insulin and ghrelin, Cummings & Overduin (2007); Duca & Covasa (2012). Among these, ghrelin is the only known orexigenic (that means: appetite stimulating) hormone, known to intensify the physiological inclination of species to hunt for food and start eating, Schwartz et al. (2000): experiments consisting in exogenous ghrelin administration support the idea that ghrelin is a physiological meal initiator, since it acts centrally to stimulate food intake, Tschöp et al. (2000); Nakazato et al. (2001); Asakawa et al. (2001).

It is known that food intake controls in feedback ghrelin production. Experiments in rats and humans clearly show that plasma ghrelin levels rise before meals and quickly decrease after food consumption, Tschöp et al. (2000); Cummings et al. (2001); Tschöp et al. (2001); Shiia et al. (2002). Although most ghrelin is produced by the stomach, a post-gastric chemosensory feedback is supposed to be required in ghrelin control, since neither gastric distension nor the presence of nutrients in the stomach lumen are required for postprandial ghrelin suppression, Tschöp et al. (2000); Shiia et al. (2002); Williams et al. (2003). More in details, Overduin et al. (2005) showed by experiments that, in mice, nutrient-related ghrelin downregulation does not necessitate the incidence of nutrients in the two-first segments of the gastrointestinal tract (i.e., stomach and duodenum), identifying the foremost physiological contribution by intestinal indicators positioned descending the ligament of Treitz, physically located between duodenum and jejunum. These experimental results were achieved in rats, and have been confirmed by experiments on humans in Parker et al. (2005), showing that intra-gastric and intra-duodenal glucose infusions suppress plasma ghrelin concentration quite equally, with the apparent delay in ghrelin suppression found out in intra-gastric glucose administration (with respect to intra-duodenal) in agreement with the time for nutrients to leave the stomach towards

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the small intestine. Instead, by varying the caloric content, keeping unaffected macronutrient distribution of meals, the intensity and time period of postprandial ghrelin suppression are dependent on the dose and the number of ingested calories: big meals inhibit ghrelin more systematically than small meals, Blom et al. (2005); Callahan et al. (2004).

Medical sciences and experimental literature have demonstrated that the majority of ghrelin release comes from the stomach (about 80%), with a secondary source in the small intestine (mostly from duodenum), Kojima et al. (1999); Date et al. (2000): experiments on rats reported in Ariyasu et al. (2001) showed that surgical elimination of the entire stomach (i.e., gastrectomy) decreases plasma ghrelin concentration by 60-80%; this result has been confirmed in humans undergoing gastric resection with a 70% reduction in circulating ghrelin, Jeon et al. (2004).

More details in ghrelin and in the experiments investigating how it regulates (and is regulated by) food intake can be found in the reviews Cummings (2006); Al Massadi et al. (2014); Müller et al. (2015) and references therein.

Ghrelin is identified as being involved in both short-term control (i.e. daily appetite control) and long-term control (metabolism of fats), Tschöp et al. (2000); Manickam & Lakshmi (2015). This note proposes a mathematical model for ghrelin, related to the daily short-term appetite control. Differently from Lakshmi & Velvizhi (2015); Manickam & Lakshmi (2015), where the modeling focus was on statistical or black-box models, here we propose a mathematical model that stems from basic and established physiological facts, highlighted in the last 15 years. The present model belongs to the wider class of dynamical models aiming at reproducing metabolism regulation (possibly involving, among the others, players like fat and fat-free mass, glucose, insulin, leptin and other food intake regulators). Though covering a specific and somehow reduced part of the problem, the present model focuses on a hormone usually ignored from the "*big picture*", except from Jacquier et al. (2014), where ghrelin dynamics is detailed within a long-term scenario involving the body weight dynamics on a horizon of weeks. In Jacquier et al. (2014) ghrelin is controlled by the energy intake, quantified by means of the available food and a "*hunger*" signal. On the other hand, here we explicitly account for the nutrients in the Gastro-Intestinal (GI) tract as responsible for the fast postprandial ghrelin suppression. The GI is coarsely modeled by a 2-compartmental system. The former tract, GI_1 ideally represented by stomach and duodenum, receives nutrients (e.g. by meals) but does not play an active role in ghrelin control; the latter tract, GI_2 ideally represented by jejunum and the first part of ileum, is responsible for signals regulating ghrelin suppression. A known feedback from nutrients in the small intestine (i.e. GI_2) triggering the release of hormones regulating the gastric emptying (i.e. GI_1) is as well considered, Brener et al. (1983); Lieverse et al. (1995); Matzinger et al. (1998). See Pires (2017) for a larger and more comprehensive literature review on energy homeostasis, appetite control and food intake.

The paper is organized as follows. Next Section is devoted to introduce the equations of the ghrelin dynamical model, with a short description of the qualitative behavior of the model solutions. Section 3 details how model parameters have been set to fit plasma ghrelin concentration samples taken from the humans' experiments reported in Cummings et al. (2001). Promising results motivate further investigation, possibly accounting for a model extension to other players involved in metabolism regulation.

2. SHORT-TERM MODEL FOR GHRELIN

The present model explicitly accounts for the gastrointestinal tract as the place where signals controlling ghrelin suppression are originated. A formal partition of the gastrointestinal part in the following 2 compartments is proposed. One embodying stomach and duodenum, both discounted to play an active role in postprandial ghrelin suppression; the other embodying jejunum and the rest of the small intestine involved in postprandial ghrelin suppression. This partition is coherent with the experimental literature that showed that ghrelin regulation is mediated by intestinal signals situated downward the ligament of Treitz, the physical junction between duodenum and jejunum (see, e.g. Williams et al. (2003); Overduin et al. (2005); Cummings (2006) and references therein). Accordingly, we denote GI_1 and GI_2 the nutrients in the two compartments, measured in litres. GI_1 empties in favor of GI_2 with no nutrients elimination, and GI_2 empties in favor of the large intestine (not modeled):

$$\begin{aligned} \frac{dGI_1}{dt} &= F(t) - f_1\big(GI_2(t)\big)GI_1(t), \\ \frac{dGI_2}{dt} &= f_1\big(GI_2(t)\big)GI_1(t) - k_{2x}GI_2(t). \end{aligned} \tag{1}$$

$F(t)$, [L/h], refers to the input of the system, modeling the food ingestion rate in the stomach, and k_{2x}, [L^{-1}], stands for the GI_2 linear clearance rate. The model accounts also for the feedback of nutrients in the small intestine triggering the production of appetite-related hormones (e.g. cholecystokinin (CCK) and glucose like peptide 1 (GLP-1)) that slow the gastric emptying, Brener et al. (1983); Lieverse et al. (1995); Matzinger et al. (1998). This feedback is modeled by the following saturating function representing the emptying rate of GI_1:

$$f_1(GI_2) = \frac{k_{12}}{1 + \sigma GI_2}, \tag{2}$$

with k_{12}, [h^{-1}], denoting the maximal emptying rate, occurring far away from meals when GI_2 is supposed to be empty and σ, [L^{-1}], quantifying the feedback action of GI_2 on GI_1 emptying rate.

Ghrelin plasma concentration, [pg/mL] is the third state variable (denoted by H), obeying to a linear clearance rate k_{hx}, [h^{-1}], with the production rate partially suppressed by GI_2. The regulating action of GI_2 is modeled by the following saturating function:

$$f_2(GI_2) = \frac{\beta}{1 + \gamma GI_2}, \tag{3}$$

with β, [pg/mL/h], denoting the maximal ghrelin production rate, far away from meals when GI_2 is supposed to be empty and γ, [L^{-1}], quantifying the inhibitory action of nutrients in GI_2 on the ghrelin production rate. In summary: