Supplementary Material

Some insights into an integrative mathematical model: a prototype-model for bodyweight and energy homeostasis

Algumas discussões em um modelo matemático integrativo: um modelo protótipo para homeostase do peso corporal e energia

Algunos debates sobre un modelo matemático integrador: un modelo prototipo para la homeostasis del peso corporal y energía

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1. Import hormones and players

1.1 Insulin

In the next scheme, it is placed alongside leptin, insulin, adiponectin, and ghrelin.

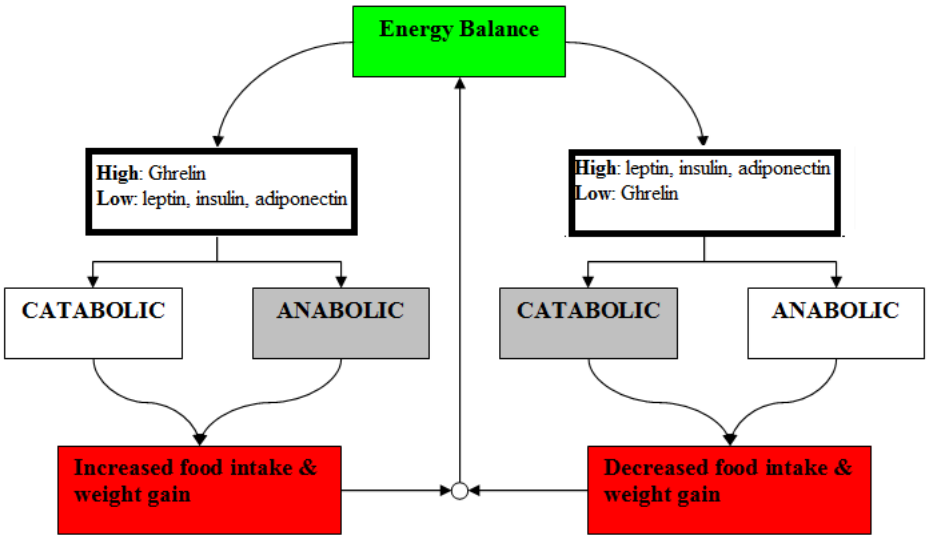

Figure 1. Energy Balance. In the third layer, white-box is the predominant process* Adapted from(1).

* This is just an intuitive scheme, for illustration only. For further details, please, see the vast literature in ghrelin. See for instance(3) for ghrelin and metabolism.

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1.2 Ghrelin

After 30 years working with peptides[2], Masayasu Kojima and co-workers were able to identify a small protein able to bind and activate efficiently an orphan receptor: this protein was ghrelin and the orphan receptor was the growth hormone secretagogue receptor (GHSR), at the present time basically called the ghrelin receptor. Ghrelin was encountered truly unexpectedly in the stomach of rats[2] and it is a relatively small (poly) peptide: 28 amino acids, compared to 51 and 167, for insulin and leptin, respectively. Furthermore, it is a powerful appetite stimulant, an orexigenic hormone, in fact the only one of its kind: it is a peripheral signal, and it is produced mainly by the stomach, in small portions in order parts such as intestines[6], brain, and pancreas. Ghrelin is an important hunger signal secreted by the stomach; it was discovered in 1999, about four years after its sister leptin. Ghrelin secretion rises between meals, when the stomach is empty, and stimulates hunger. As the stomach fills during a meal, the secretion of ghrelin rapidly falls off and hunger is thereby reduced. However, one recent study demonstrated raised levels of ghrelin in dieters who lost weight. If this raised ghrelin level enhances appetite, it may partially explain why it is so difficult for most dieters to maintain their weight loss. It is produced by several points within the body such as pancreas (ε-cells), stomach, and heart[4].

1.3 (Poly) Peptide YY

A recently discovered hormone secreted by the small intestine, named polypeptide YY (PYY), regulates hunger on a more intermediate-time basis. See scheme in figure 2. Basically it is reported to count glucose absorption, it inhibits the intake of food; therefore, opposing ghrelin and supporting leptin and insulin.

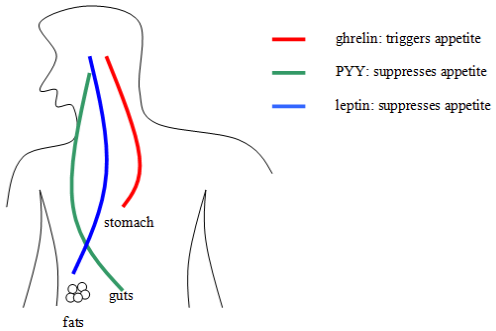

Figure 2. Three hormones working on the appetite control. Source: own elaboration.

The intestinal satiety hormones, including CCK (cholecystokinin), PYY, glucagon-like peptide-1 (GLP-1) and others, are believed to stimulate sensory neurons of the vagus nerve, which communicate the satiety signals to the CNS (*Central Nervous System*).

1.4 Cholecystokinin

Another hormone that regulates eating is the intestinal hormone cholecystokinin (CCK)[*]. Secretion of CCK rises during and immediately after a meal and suppresses hunger (promotes satiety/satiation). CCK thus acts antagonistically to ghrelin, helping to moderate satiety immediately after a meal. Cholecystokinin is a hormone produced primarily in the duodenum and jejunum, parts of the small intestine, but also in the brain. It decreases meal size[(7)]. Cummings and Overduin[(8)] note that CCK is involved in short-term satiation, acutely shortening mealtime, rather than long-term control. Further, leptin works alongside CCK to stimulate vagal afferents that indicate gastrointestinal satiation to the brain[(6)].

[*] This hormone was the one responsible for the discovery of leptin, it was thought CCK played the role on regulating food intake now granted to leptin and ghrelin.

1.5 Amylin

Amylin is a peptide hormone also secreted after meals, alongside with insulin, by the beta cells of the pancreas. Amylin inhibits the stomach from emptying, as well as inhibiting gastric acid and glucagon secretion[(7)]. It has the capacity to reduce food intake and meal size[(7)]. Amylin is secreted in proportion to food intake and can be considered a hormone of satiety[(7)]. Furthermore, amylin does cross the blood-brain barrier and works directly on certain areas of the brain, and is considered a neuro-endocrine hormone[(7)].

1.6 Somatostatin

In the pancreas, somatostatin is produced by the delta cells of the islets of Langerhans[(9)], where it serves to block the secretion of both insulin and glucagon from adjacent cells. Insulin, glucagon, and somatostatin act in concert to control the flow of nutrients into and out of the circulation[(11)]. Further, it is also produced by the hypothalamus and intestine[(9)].

1.7 Glucagon like peptide (GLP-1)

Glucagon like peptide (GLP-1) is a very powerful stimulator of insulin secretion

from the pancreatic islets[9]. GLP-1 is released in response to meal intake[12]. GLP-1 also appears to be a physiological regulator of appetite and food intake[12]. The stimulation of leptin or insulin receptors on enteroendocrine cells enhances GLP-1 secretion. This shows an important synergetic behaviour: short- and long-acting catabolic signals occurring in the gut[13].

1.8 Neuropeptide Y

Neuropeptide Y is one of the most prevalent peptides throughout the brain (including the hypothalamus) and even the sympathetic nervous system. It stimulates feeding behavior and weight gain[7]. Notably, both insulin and leptin, which decrease food intake, inhibit neuropeptide Y[9], and fasting increases its levels. Ghrelin, on the other hand, induces its production.

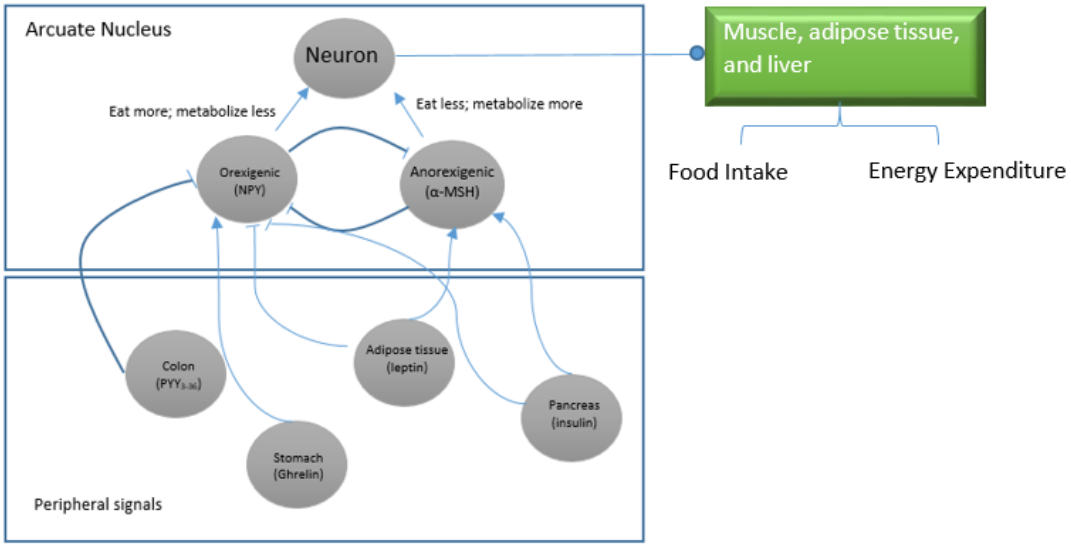

Figure 3. Neuropeptide Y in the food intake/appetite control machinery. In the arcuate nucleus (hypothalamus), we two agglomerates of neurons: orexigenic – releases neuropeptide y; anorexigenic – releases α-Melanocyte-stimulating hormone. Those signals influence the proper neighboring neurons for the "message" to go on: hunger and metabolism control. Source: based on[10, p.932].

1.9 Adiponectin

Adipocytes have been found to secrete regulatory molecules, collectively termed adipokines, which regulate hunger, metabolism, and insulin sensitivity[9]. One of those adipokines is called adiponectin. Adiponectin, discovered in the 1990s, is an amino acid protein hormone that is secreted in

adipose tissue but found circulating in blood[7]. In contrast to levels of leptin, which are higher in obese people, levels of adiponectin are significantly lower in obese individuals[7]. Furthermore, levels are lower in people who have insulin resistance, that is, those with high levels of insulin and abnormal glucose tolerance test results[7]. At least in animals, administration of adiponectin is known to enhance the action of insulin, and it has been found to lower circulating levels of glucose[7].

2. Remarks

As it can be seen, the functions and roles seem fuzzy, most hormones seem to be doing the same undertaking. The key challenge from a mathematical modeling standpoint is how to separate properly the workings of each hormone. One possibility is quite simple: like in the net force, we have several players, but just one appears, an imaginary force, which is coordinated by all of the hormones. If so, the question is how to project each component on such a way to see clearly the contribution of each of them.

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